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BICYCLIC PYRIMIDINE MATRIX METALLOPROTEINASE INHIBITORS

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BICYCLIC PYRIMIDINE MATRIX METALLOPROTEINASE INHIBITORS**CROSS-REFERENCE TO RELATED APPLICATIONS**

This application claims benefit of priority from United States provisional application no. 60/268,780, filed February 14, 2001.

5

FIELD OF THE INVENTION

This invention relates to a group of bicyclic pyrimidine derivatives which inhibit matrix metalloproteinase enzymes and thus are useful for treating diseases resulting from tissue breakdown, such as heart disease, multiple sclerosis, arthritis, atherosclerosis, and osteoporosis.

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BACKGROUND OF THE INVENTION

Matrix metalloproteinases (sometimes referred to as MMPs) are naturally-occurring enzymes found in most mammals. Over-expression and activation of MMPs or an imbalance between MMPs and inhibitors of MMPs have been suggested as factors in the pathogenesis of diseases characterized by the breakdown of extracellular matrix or connective tissues.

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Stromelysin-1 and gelatinase A are members of the matrix

metalloproteinases (MMP) family. Other members include fibroblast collagenase (MMP-1), neutrophil collagenase (MMP-8), gelatinase B (92 kDa gelatinase) (MMP-9), stromelysin-2 (MMP-10), stromelysin-3 (MMP-11), matrilysin

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(MMP-7), collagenase 3 (MMP-13), TNF-alpha converting enzyme (TACE), and other newly discovered membrane-associated matrix metalloproteinases (Sato H, Takino T, Okada Y, Cao J, Shinagawa A, Yamamoto E, and Seiki M., *Nature*, 1994;370:61-65). These enzymes have been implicated with a number of diseases which result from breakdown of connective tissue, including such diseases as rheumatoid arthritis, osteoarthritis, osteoporosis, periodontitis, multiple sclerosis, gingivitis, corneal epidermal and gastric ulceration, atherosclerosis, neointimal

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proliferation which leads to restenosis and ischemic heart failure, and tumor metastasis. A method for preventing and treating these and other diseases is now recognized to be by inhibiting metalloproteinase enzymes, thereby curtailing and/or eliminating the breakdown of connective tissues that results in the disease

5 states.

The catalytic zinc in matrix metalloproteinases is typically the focal point for inhibitor design. The modification of substrates by introducing zinc chelating groups has generated potent inhibitors such as peptide hydroxamates and thiol-containing peptides. Peptide hydroxamates and the natural endogenous inhibitors
10 of MMPs (TIMPs) have been used successfully to treat animal models of cancer and inflammation. MMP inhibitors have also been used to prevent and treat congestive heart failure and other cardiovascular diseases, United States Patent Number 5,948,780.

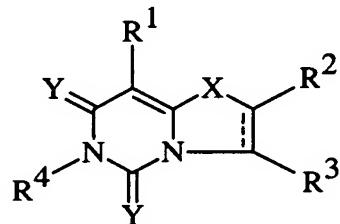
A major limitation on the use of currently known MMP inhibitors is their
15 lack of specificity for any particular enzyme. Recent data has established that specific MMP enzymes are associated with some diseases, with no effect on others. The MMPs are generally categorized based on their substrate specificity, and indeed the collagenase subfamily of MMP-1, MMP-8, and
20 MMP-13 selectively cleave native interstitial collagens, and thus are associated only with diseases linked to such interstitial collagen tissue. This is evidenced by the recent discovery that MMP-13 alone is over expressed in breast carcinoma, while MMP-1 alone is over expressed in papillary carcinoma (see Chen et al.,
J. Am. Chem. Soc., 2000;122:9648-9654).

There appears to be few selective inhibitors of MMP-13 reported.
25 A compound named WAY-170523 has been reported by Chen et al., *supra.*, 2000, and a few other compounds are reported in PCT international patent application Number WO 01/63244 A1, as allegedly selective inhibitors of MMP-13. Further, United States Patent Number 6,008,243 discloses inhibitors of MMP-13.
30 However, no selective or nonselective inhibitor of MMP-13 has been approved and marketed for the treatment of any disease in any mammal. Accordingly, the need continues to find new low molecular weight compounds that are potent and selective MMP inhibitors, and that have an acceptable therapeutic index of toxicity/potency to make them amenable for use clinically in the prevention and

treatment of the associated disease states. An object of this invention is to provide a group of selective MMP-13 inhibitor compounds characterized as being bicyclic pyrimidines.

SUMMARY OF THE INVENTION

5 This invention provides a group of bicyclic pyrimidine compounds that are inhibitors of matrix metalloproteinase enzymes, and especially MMP-13. The invention is more particularly directed to compounds defined by Formula I



or a pharmaceutically acceptable salt thereof,

10 wherein:

“---” is absent or is a bond;

X is O, S, SO, SO₂, CH₂, C = O, CHOH, NH, or NR⁵;

Y is O or S;

R¹ is H, (O)_nC₁-C₆ alkyl, (O)_n substituted C₁-C₆ alkyl, NO₂, NR⁵R⁶, CHO, or

15 halo;

R², R³, and R⁴ independently are hydrogen, halo, C₁-C₆ alkyl, substituted C₁-C₆ alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, C₂-C₁₀ alkynyl, substituted C₂-C₁₀ alkynyl, (CH₂)_m OH, (CH₂)_m OR⁵, (CH₂)_m cycloalkyl, (CH₂)_m substituted cycloalkyl, CHOH (CH₂)_m aryl, CHOH

20 (CH₂)_m substituted aryl, CHOH (CH₂)_m heteroaryl, CHOH (CH₂)_m substituted heteroaryl, (CO₂)_n(CH₂)_m aryl, (CO₂)_n(CH₂)_m substituted aryl, (CO₂)_n(CH₂)_m heteroaryl, (CO₂)_n(CH₂)_m substituted heteroaryl, (CO₂)_n(CH₂)_m carbocycle, (CO₂)_n(CH₂)_m substituted carbocycle,

(CO₂)_n(CH₂)_m heterocycle, (CO₂)_n(CH₂)_m substituted heterocycle,
10 (CO₂)_n(CH₂)_m NR⁵R⁶, CH(C₁-₆ alkyl)-aryl, (CH₂)_m N(H) C(=O)aryl,
15 (CH₂)_m-S(O)₀₋₂-(CH₂)_n-aryl, CH(C₁-C₆ alkyl)-substituted aryl,
20 (CH₂)_mN(H) C(=O) substituted aryl, (CH₂)_m-S(O)₀₋₂-(CH₂)_n substituted
25 aryl,
C(=O)N(R⁵)-(CH₂)_m aryl, C(=O)N(R⁵)-(CH₂)_m substituted aryl,
NH
||
10 C(=O)N(R⁵)-(CH₂)_m heteroaryl, C(=O)N(R⁵)-(CH₂)_m substituted
heteroaryl, C≡C-(CH₂)_m aryl, C≡C-(CH₂)_m substituted aryl,
15 C≡C-(CH₂)_m-heteroaryl, C≡C-(CH₂)_m substituted heteroaryl,
C≡C-(CH₂)_m carbocycle, C≡C-(CH₂)_m substituted carbocycle,
20 (CH₂)_m-O-aryl, (CH₂)_m-O-substituted aryl, (CH₂)_m COR⁵,
S
||
15 (CH₂)_m CONR⁵R⁶, (CH₂)_m CNR⁵R⁶,
20 or (CH₂)_m CO₂R⁵;
m is an integer from 0 to 6;
25 R⁵ and R⁶ independently are hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl,
(CH₂)_m aryl, (CH₂)_m substituted aryl, (CH₂)_m heteroaryl or (CH₂)_m
substituted heteroaryl, or R⁵ and R⁶ are taken together with the nitrogen
atom to which they are attached complete a 3- to 7-membered ring;
containing carbon atoms, the nitrogen atom bearing R⁵ and R⁶, and
30 optionally 1 or 2 heteroatoms independently selected form O, S, and NR²,
wherein R² is as defined above and;
n is 0 or 1; with the proviso that R² and R⁴ are not both selected from hydrogen
and C₁-C₆ alkyl.

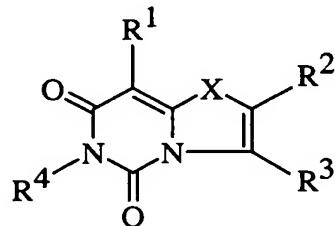
Another invention embodiment is compounds of Formula I, or a pharmaceutically acceptable salt thereof, wherein X is S, SO, or SO₂, and Y, R¹, R², R³, and R⁴ are as defined above.

5 Another invention embodiment is compounds of Formula I, or a pharmaceutically acceptable salt thereof, wherein R² and R⁴ are not H.

Another invention embodiment is compounds of Formula I, or a pharmaceutically acceptable salt thereof, wherein R³ is H or fluoro, and both R² and R⁴ are not H.

10 Another invention embodiment is compounds of Formula I, or a pharmaceutically acceptable salt thereof, that have R² equal CO₂ aryl or CO₂ heteroaryl, wherein aryl and heteroaryl may be unsubstituted or substituted.

Another invention embodiment is compounds of Formula II



II

15 or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³, R⁴, and X are as defined above.

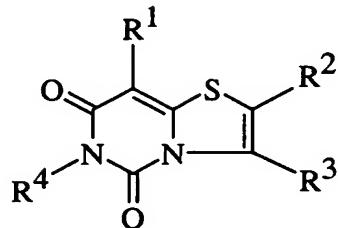
Another invention embodiment is compounds of Formula II, or a pharmaceutically acceptable salt thereof, wherein R¹ is H or CH₃, R² is CO₂CH₂ aryl, CO₂CH₂ heteroaryl, CONHCH₂ aryl, or CONHCH₂ heteroaryl, wherein the aryl and heteroaryl groups are unsubstituted or substituted, and R³ is 20 H or fluoro.

Also another invention embodiment is compounds of Formula II, or a pharmaceutically acceptable salt thereof, that are amides, i.e., compounds



25 wherein R² is (CH₂)_m CNR⁵R⁶.

Another invention embodiment is compounds of Formula III



III

or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³, and R⁴ are as defined above.

5 Another invention embodiment is compounds of Formula III, or a pharmaceutically acceptable salt thereof, where R² is CO₂CH₂ aryl, CO₂CH₂ heteroaryl, CONHCH₂ aryl, or CONHCH₂ heteroaryl, wherein the aryl and heteroaryl groups are unsubstituted or substituted, R³ is H, and R⁴ is CH₂ aryl, CH₂ substituted aryl, CH₂ heteroaryl, or CH₂ substituted heteroaryl.

10 Another invention embodiment is a compound of Formula III, or a pharmaceutically acceptable salt thereof, selected from:

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carbothioic acid benzylamide; and

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carbothioic acid 4-methoxy-benzylamide.

Another invention embodiment is a compound of Formula III, or a pharmaceutically acceptable salt thereof, named:

6-Benzyl-2-(3-phenyl-propionyl)-thiazolo[3,2-c]pyrimidine-5,7-dione;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-

20 2-carboxylic acid prop-2-ynylamide;

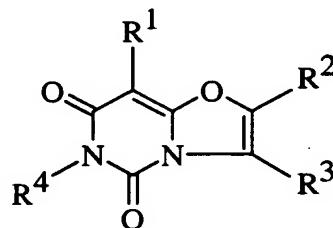
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (piperidin-4-ylmethyl)-amide hydrochloride;

Another invention embodiment is a compound of Formula III, or a pharmaceutically acceptable salt thereof, selected from:

25 6-Benzyl-2-(1-hydroxy-3-phenyl-allyl)-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione;

6-Benzyl-2-(1-hydroxy-3-phenyl-prop-2-ynyl)-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione;
6-Benzyl-2-(hydroxy-phenyl-methyl)-thiazolo[3,2-c]pyrimidine-5,7-dione;
and
5 6-Benzyl-2-(1-hydroxy-3-phenyl-propyl)-thiazolo[3,2-c]pyrimidine-5,7-dione.

Another invention embodiment is compounds that have Formula IV



IV

or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³, and R⁴ are as
10 defined above.

Another invention embodiment is a compound of Formula IV, or a pharmaceutically acceptable salt thereof, selected from:

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-oxazolo[3,2-c]pyrimidine-2-carboxylic acid benzyl ester; and

15 6-Benzyl-5,7-dioxo-6,7-dihydro-5H-oxazolo[3,2-c]pyrimidine-2-carboxylic acid benzyl ester.

Another invention embodiment is a compound of Formula IV, or a pharmaceutically acceptable salt thereof, selected from:

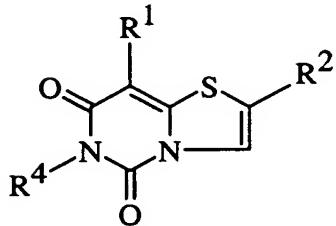
20 6-Benzyl-5,7-dioxo-6,7-dihydro-5H-oxazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-oxazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-oxazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide; and

25 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-oxazolo[3,2-c]pyrimidine-2-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide.

Another invention embodiment is compounds that have Formula V



V

or a pharmaceutically acceptable salt thereof, wherein R¹ is hydrogen, (O)_n C₁-

C₆ alkyl, or (O)_n substituted C₁-C₆ alkyl, R² is CO₂(CH₂)_m aryl,

CO₂(CH₂)_m substituted aryl,

NH

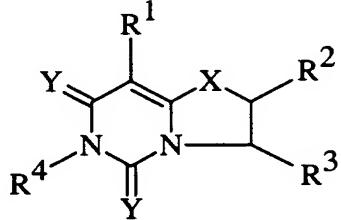
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R⁴ is (CH₂)_m CO₂R⁵, (CH₂)_m CONR⁵R⁶, (CH₂)_m CNR⁵R⁶, CHOH
(CH₂)_m aryl, CHOH (CH₂)_m substituted aryl, CHOH (CH₂)_m heteroaryl,

CHOH (CH₂)_m substituted aryl. Preferred compounds of Formula V are
those wherein m is 0 or 1.

Another invention embodiment are 2,3-dihydro compounds of

Formula VI:



VI

or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³, R⁴, Y, and X
are as defined above.

Another invention embodiment is a compound of Formula VI, or a
pharmaceutically acceptable salt thereof, selected from:

6-Benzyl-8-methyl-5,7-dioxo-1,5,6,7-tetrahydro-imidazo[1,2-c]pyrimidine-2-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide;

6-Benzyl-1,8-dimethyl-5,7-dioxo-1,5,6,7-tetrahydro-imidazo[1,2-c]pyrimidine-2-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide;

6-Benzyl-1,8-dimethyl-5,7-dioxo-1,5,6,7-tetrahydro-imidazo[1,2-c]pyrimidine-2-carboxylic acid benzylamide;

6-Benzyl-1,8-dimethyl-5,7-dioxo-1,5,6,7-tetrahydro-imidazo[1,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide;

5 6-Benzyl-1-methyl-5,7-dioxo-1,5,6,7-tetrahydro-imidazo[1,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide;

6-(4-Methoxy-benzyl)-1-methyl-5,7-dioxo-1,5,6,7-tetrahydro-imidazo[1,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide; and

6-(4-Methoxy-benzyl)-1,8-dimethyl-5,7-dioxo-1,5,6,7-tetrahydro-imidazo[1,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide.

10 Another invention embodiment is a compound of Formula VI, or a pharmaceutically acceptable salt thereof, selected from:

6-Benzyl-5,7-dioxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzyl ester 2,3-Dihydroxypropionic acid benzyl ester;

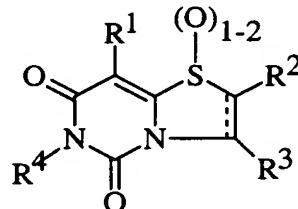
15 6-Benzyl-5,7-dioxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid pyridin-4-ylmethyl ester hydrochloride;

6-Benzyl-1,5,7-trioxo-1,2,3,5,6,7-hexahydro-1*H*-thiazolo[3,2-c]pyrimidine-3-carboxylic acid benzyl ester; and

6-Benzyl-1,8-dimethyl-5,7-dioxo-1,5,6,7-tetrahydro-imidazo[1,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzyl ester.

Another invention embodiment is a compound of Formula VI, or a pharmaceutically acceptable salt thereof, named 6-benzyl-3-ethoxy-2,3-dihydro-oxazolo[3,2-c]pyrimidine-5,7-dione.

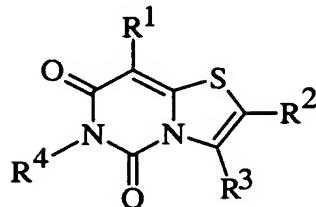
Another invention embodiment is sulfoxides and sulfones of Formula VII



VII

or a pharmaceutically acceptable salt thereof, wherein R¹, R², R³, and R⁴ are as defined above.

Another invention embodiment is a compound of Formula I of
Formula VIII



VIII

or a pharmaceutically acceptable salt thereof, wherein:

5 R^1 is H, CH_3 , CH_2OH , or CHO ;

10 R^2 is $(CO_2)(CH_2)_m$ aryl, $(CO_2)(CH_2)_m$ substituted aryl, $(CO_2)(CH_2)_m$ heteroaryl, $(CO_2)(CH_2)_m$ substituted heteroaryl, $C(=O)N(R^5)-(CH_2)_m$ -aryl, $C(=O)N(R^5)-(CH_2)_m$ substituted aryl, $C(=O)N(R^5)-(CH_2)_m$ heteroaryl, $C(=O)N(R^5)-(CH_2)_m$ substituted heteroaryl, $C\equiv C-(CH_2)_m$ aryl, $C\equiv C-(CH_2)_m$ substituted aryl, $C\equiv C-(CH_2)_m$ heteroaryl, or $C\equiv C-(CH_2)_m$ substituted heteroaryl, wherein

15 R^5 is hydrogen or methyl;

20 R^3 is hydrogen or fluoro;

25 R^4 is C_2-C_6 alkenyl, substituted C_2-C_6 alkenyl, C_1-C_6 alkyl, substituted C_1-C_6 alkyl, C_2-C_{10} alkenyl, substituted C_2-C_{10} alkenyl, $(CH_2)_mCOR^5$, $(CH_2)_mS(O)_{0-2}(CH_2)_n$ aryl, $C(=O)N(R^5)-CH_2)_m$ aryl, $(CH_2)_m-O$ -aryl, $(CH_2)_mS(O)_{0-2}(CH_2)_n$ substituted aryl, $C(=O)N(R^5)-CH_2)_m$ substituted aryl, $(CH_2)_m-O$ -substituted aryl, $(CO_2)_n(CH_2)_m$ aryl, $(CO_2)_n(CH_2)_m$ substituted aryl, $(CO_2)_n(CH_2)_m$ heteroaryl, $(CO_2)_n(CH_2)_m$ substituted heteroaryl, $(CO_2)_n(CH_2)_m$ carbocycle, or $(CO_2)_n(CH_2)_m$ substituted carbocycle, wherein

30 n is 0 or 1;

35 m is an integer of from 0 to 6; and

40 R^5 is as defined above for Formula I.

Another invention embodiment is a compound of Formula VIII, or a pharmaceutically acceptable salt thereof, wherein:

R¹ is H or CH₃;

R² is C(=O)N(R⁵)-(CH₂)_m aryl, C(=O)N(R⁵)-(CH₂)_m substituted aryl,

5 C(=O)N(R⁵)-(CH₂)_m heteroaryl, C(=O)N(R⁵)-(CH₂)_m substituted heteroaryl, C≡C-(CH₂)_m aryl, C≡C-(CH₂)_m substituted aryl, C≡C-(CH₂)_m heteroaryl, or C≡C-(CH₂)_m substituted heteroaryl, wherein

R⁵ is H or methyl;

R³ is hydrogen or fluoro;

10 R⁴ is (CO₂)_n(CH₂)_m aryl, (CO₂)_n(CH₂)_m substituted aryl, (CO₂)_n(CH₂)_m heteroaryl, (CO₂)_n(CH₂)_m substituted heteroaryl, (CO₂)_n(CH₂)_m carbocycle, or (CO₂)_n(CH₂)_m substituted carbocycle, wherein:

n is 0 or 1, and

m is an integer of from 0 to 6.

15 Another invention embodiment is a compound of Formula VIII, or a pharmaceutically acceptable salt thereof, wherein:

R¹ is H or CH₃;

R² is C≡C-(CH₂)_m aryl, C≡C-(CH₂)_m substituted aryl, C≡C-(CH₂)_m heteroaryl, or C≡C-(CH₂)_m substituted heteroaryl, wherein:

20 m is 1;

R₃ is hydrogen or fluoro; and

R₄ is (CO₂)_n(CH₂)_m aryl, (CO₂)_n(CH₂)_m substituted aryl, (CO₂)_n(CH₂)_m heteroaryl, (CO₂)_n(CH₂)_m substituted heteroaryl, (CO₂)_n(CH₂)_m carbocycle, or (CO₂)_n(CH₂)_m substituted carbocycle,

25 wherein n is 0 and m is 1.

Another invention embodiment is a compound of Formula VIII, or a pharmaceutically acceptable salt thereof, wherein:

R₁ is H or CH₃;

R₂ is C(=O)N(R⁵)-(CH₂)_maryl, C(=O)N(R⁵)-(CH₂)_msubstituted aryl,

C(=O)N(R⁵)-(CH₂)_mheteroaryl, or C(=O)N(R⁵)-(CH₂)_msubstituted heteroaryl,

wherein m is 1 and R⁵ is H or CH₃;

5 R³ is hydrogen or fluoro; and

R⁴ is (CO₂)_n(CH₂)_maryl, (CO₂)_n(CH₂)_msubstituted aryl,

(CO₂)_n(CH₂)_mheteroaryl, (CO₂)_n(CH₂)_msubstituted heteroaryl,

(CO₂)_n(CH₂)_mcarbocycle, or (CO₂)_n(CH₂)_msubstituted carbocycle,

wherein n is 0 and m is 1;

10 Another invention embodiment is a compound of Formula VIII, or a pharmaceutically acceptable salt thereof, selected from:

4-[8-Methyl-5,7-dioxo-2-(3-phenyl-prop-1-ynyl)-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid;

4-{2-[3-(4-Methoxy-phenyl)-prop-1-ynyl]-8-methyl-5,7-dioxo-7H-

15 thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid;

4-{2-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid;

4-{2-[3-(3-Methoxy-phenyl)-prop-1-ynyl]-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid;

20 4-{2-[3-(3,4-Difluoro-phenyl)-prop-1-ynyl]-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid;

6-Benzyl-8-methyl-2-(3-pyridin-4-yl-prop-1-ynyl)-thiazolo[3,2-c]pyrimidine-5,7-dione;

6-(3,4-Dichloro-benzyl)-8-methyl-2-(3-pyridin-4-yl-prop-1-ynyl)-

25 thiazolo[3,2-c]pyrimidine-5,7-dione;

6-(3,4-Dichloro-benzyl)-2-[3-(2-methoxy-pyridin-4-yl)-prop-1-ynyl]-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione;

6-Benzyl-8-methyl-2-phenylethynyl-thiazolo[3,2-c]pyrimidine-5,7-dione;

6-(4-Bromo-benzyl)-2-[3-(3-methoxy-phenyl)-prop-1-ynyl]-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione;

4-{2-[3-(3-Methoxy-phenyl)-prop-1-ynyl]-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzenesulfonamide;

4-{2-[3-(3-Fluoro-4-methoxy-phenyl)-prop-1-ynyl]-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid;

5 6-(4-Fluoro-benzyl)-8-methyl-2-(3-phenyl-prop-1-ynyl)-thiazolo[3,2-c]pyrimidine-5,7-dione;

6-Benzyl-8-methyl-2-(3-phenyl-prop-1-ynyl)-thiazolo[3,2-c]pyrimidine-5,7-dione;

10 6-(3,4-Dichloro-benzyl)-2-[3-(3-methoxy-phenyl)-prop-1-ynyl]-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione;

6-(4-Methanesulfonyl-benzyl)-8-methyl-2-(3-pyridin-4-yl-prop-1-ynyl)-thiazolo[3,2-c]pyrimidine-5,7-dione;

15 4-{2-[3-(3-Methoxy-phenyl)-prop-1-ynyl]-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzonitrile;

4-[8-Methyl-5,7-dioxo-2-(3-phenyl-prop-1-ynyl)-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid;

20 2-[3-(3-Methoxy-phenyl)-prop-1-ynyl]-8-methyl-6-[4-(2H-tetrazol-5-yl)-benzyl]-thiazolo[3,2-c]pyrimidine-5,7-dione;

6-Benzyl-2-[3-(3-methoxy-phenyl)-prop-1-ynyl]-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione;

25 6-Benzyl-8-methyl-2-(3-phenyl-prop-1-ynyl)-thiazolo[3,2-c]pyrimidine-5,7-dione;

2-[3-(3-Methoxy-phenyl)-prop-1-ynyl]-8-methyl-6-[4-(morpholine-4-carbonyl)-benzyl]-thiazolo[3,2-c]pyrimidine-5,7-dione;

8-Methyl-6-[4-(morpholine-4-sulfonyl)-benzyl]-2-(3-pyridin-4-yl-prop-1-ynyl)-thiazolo[3,2-c]pyrimidine-5,7-dione;

30 2-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-8-methyl-6-(2-oxo-2H-1-benzopyran-6-ylmethyl)-thiazolo[3,2-c]pyrimidine-5,7-dione;

2-[3-(3-Methoxy-phenyl)-prop-1-ynyl]-8-methyl-6-(2-oxo-2H-1-benzopyran-6-ylmethyl)-thiazolo[3,2-c]pyrimidine-5,7-dione;

4-[8-Methyl-5,7-dioxo-2-(4-phenyl-but-1-ynyl)-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid;

4-[8-Methyl-5,7-dioxo-2-(6-phenyl-hex-1-ynyl)-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid;

4-[8-Methyl-5,7-dioxo-2-(5-phenyl-pent-1-ynyl)-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid;

5 4-[8-Methyl-5,7-dioxo-2-(7-phenyl-hept-1-ynyl)-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid;

(4-{2-[3-(3,4-Difluoro-phenyl)-prop-1-ynyl]-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-phenyl)-acetic acid;

10 6-(3-Fluoro-benzyl)-8-methyl-2-(3-pyridin-4-yl-prop-1-ynyl)-thiazolo[3,2-c]pyrimidine-5,7-dione;

6-(3,4-Difluoro-benzyl)-8-methyl-2-(3-pyridin-4-yl-prop-1-ynyl)-thiazolo[3,2-c]pyrimidine-5,7-dione;

6-(3-Fluoro-benzyl)-2-[3-(2-methoxy-pyridin-4-yl)-prop-1-ynyl]-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione;

15 [3-(8-Methyl-5,7-dioxo-2-phenylethynyl)-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-phenyl]-acetic acid;

6-(4-Bromo-benzyl)-2-[3-(4-fluoro-3-methoxy-phenyl)-prop-1-ynyl]-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione;

4-{2-[3-(3-Methoxy-phenyl)-prop-1-ynyl]-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-N,N-dimethyl-benzenesulfonamide;

20 4-{2-[3-(3-Fluoro-4-methoxy-phenyl)-prop-1-ynyl]-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-cyclohexanecarboxylic acid;

6-(3,4-Difluoro-benzyl)-2-[3-(3,4-difluoro-phenyl)-prop-1-ynyl]-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione;

25 4-[8-Methyl-5,7-dioxo-2-(3-phenyl-prop-1-ynyl)-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-cyclohexanecarboxylic acid;

2-Chloro-4-{2-[3-(3-methoxy-phenyl)-prop-1-ynyl]-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid;

30 2-[3-(4-Fluoro-phenyl)-prop-1-ynyl]-6-(4-methanesulfonyl-benzyl)-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione;

4-{2-[3-(4-Fluoro-3-methoxy-phenyl)-prop-1-ynyl]-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzonitrile;

(3-{2-[3-(4-Fluoro-3-methoxy-phenyl)-prop-1-ynyl]-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-phenyl)-acetic acid;

(4-{2-[3-(3-Methoxy-phenyl)-prop-1-ynyl]-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-phenyl)-acetic acid;

5 6-(3,4-Difluoro-benzyl)-8-methyl-2-(3-phenyl-prop-1-ynyl)-thiazolo[3,2-c]pyrimidine-5,7-dione;

 2-[3-(3-Methoxy-phenyl)-prop-1-ynyl]-8-methyl-6-[4-(thiomorpholine-4-carbonyl)-benzyl]-thiazolo[3,2-c]pyrimidine-5,7-dione;

10 8-Methyl-2-(3-pyridin-4-yl-prop-1-ynyl)-6-[4-(thiomorpholine-4-sulfonyl)-benzyl]-thiazolo[3,2-c]pyrimidine-5,7-dione;

 2-[3-(4-Fluoro-3-methoxy-phenyl)-prop-1-ynyl]-8-methyl-6-(2-oxo-2H-1-benzopyran-6-ylmethyl)-thiazolo[3,2-c]pyrimidine-5,7-dione; and

 2-[3-(3-Methoxy-4-methyl-phenyl)-prop-1-ynyl]-8-methyl-6-(2-oxo-2H-1-benzopyran-6-ylmethyl)-thiazolo[3,2-c]pyrimidine-5,7-dione.

15 Another invention embodiment is a compound of Formula VIII, or a pharmaceutically acceptable salt thereof, selected from:

 6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide;

20 6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid biphenyl-4-ylamide;

 6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride;

 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-fluoro-benzylamide;

25 6-Benzoyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide;

 6-(3,4-Dichloro-benzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide;

30 6-(4-Chloro-benzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide;

 6-(4-Chloro-benzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-dichloro-benzylamide;

5,7-Dioxo-6-pyridin-4-ylmethyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide hydrochloride;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide;

5 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-dichlorobenzylamide;

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride;

10 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 2,4-dichloro-benzylamide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-methyl-benzylamide;

15 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

6-Benzyl-8-formyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (1H-indol-5-ylmethyl)-amide;

20 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (thiazol-4-ylmethyl)-amide hydrochloride;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride;

25 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide hydrochloride;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (imidazo[2,1-b]thiazol-6-ylmethyl)-amide;

30 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (1-methyl-1H-pyrazol-4-ylmethyl)-amide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-2-ylmethyl)-amide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2,1,3-benzothiadiazol-5-ylmethyl)-amide;

5 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-difluoro-benzylamide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide;

10 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide hydrochloride;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-fluoro-4-methoxy-benzylamide;

15 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-2-ylmethyl)-amide hydrochloride;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methyl-benzylamide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-trifluoromethyl-benzylamide;

20 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-chloro-benzylamide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-trifluoromethoxy-benzylamide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-thiazol-4-ylmethyl)-amide hydrochloride;

25 4-[2-(4-Methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid;

4-[2-(4-Methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid Sodium salt;

4-[2-(4-Methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester hydrochloride;

30 4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid;

4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid Sodium salt;

4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester;

5 4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester hydrochloride;

 4-{8-Methyl-5,7-dioxo-2-[(pyridin-4-ylmethyl)-carbamoyl]-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid trifluoro-acetic acid salt;

 4-{8-Methyl-5,7-dioxo-2-[(pyridin-4-ylmethyl)-carbamoyl]-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid 2-dimethylamino-ethyl ester

10 dihydrochloride;

 8-Methyl-6-(2-methyl-thiazol-4-ylmethyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

 2-Chloro-4-[2-(4-fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester;

15 8-Methyl-5,7-dioxo-6-(2H-tetrazol-5-ylmethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

 8-Methyl-5,7-dioxo-6-thiazol-2-ylmethyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide hydrochloride;

20 4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-2-methyl-benzoic acid methyl ester;

 4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-2-methoxy-benzoic acid methyl ester;

 6-(4-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride;

25 6-(4-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride;

 6-(4-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride;

30 8-Methyl-6-[4-(morpholine-4-carbonyl)-benzyl]-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride;

(5-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-isoxazol-3-yl}-carbamic acid methyl ester;

8-Methyl-5,7-dioxo-6-[4-(2H-tetrazol-5-yl)-benzyl]-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

8-Methyl-6-[4-(morpholine-4-carbonyl)-benzyl]-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

6-(6-Fluoro-quinolin-2-ylmethyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

2-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-5-methoxy-pyrimidine-4-carboxylic acid methyl ester;

6-But-2-ynyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

8-Methyl-5,7-dioxo-6-(2-oxo-2H-1-benzopyran-6-ylmethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

6-(4-Methanesulfonyl-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride;

6-(3-Cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride;

6-[2-(4-Chloro-benzenesulfonyl)-ethyl]-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride;

8-Methyl-5,7-dioxo-6-(4-sulfamoyl-benzyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride;

6-(4-Cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride;

8-Methyl-5,7-dioxo-6-(3-oxo-3-phenyl-propyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

8-Methyl-5,7-dioxo-6-(1-phenyl-ethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

8-Methyl-5,7-dioxo-6-(2-phenylmethanesulfonyl-ethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

6-(5-Cyano-pentyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

6-(E)-But-2-enyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

5 8-Methyl-5,7-dioxo-6-(E)-pent-2-enyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

6-sec-Butyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

6-(2-Benzenesulfonyl-ethyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

10 6-(1-Ethyl-propyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

8-Methyl-5,7-dioxo-6-pent-2-ynyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

15 6-(2-Benzenesulfonyl-ethyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

8-Methyl-6-(3-methyl-but-2-enyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

6-[2-(4-Fluoro-benzenesulfonyl)-ethyl]-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

20 6-[3-(4-Fluoro-phenyl)-3-oxo-propyl]-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

6-(2-Benzoylamino-ethyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

25 8-Methyl-5,7-dioxo-6-(2-phenoxy-ethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

6-(3,4-Dichloro-benzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide;

30 6-(4-Cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-methoxy-benzylamide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (tetrahydro-furan-2-ylmethyl)-amide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide;

5 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-fluoro-benzylamide;

 6-(3-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-fluoro-benzylamide;

10 6-(3,4-Dichloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide;

 6-(3,4-Dichloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methyl-benzylamide;

 8-Methyl-5,7-dioxo-6-pyridin-4-ylmethyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide;

15 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide;

 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide;

 6-(4-Methoxy-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide;

20 8-Methyl-5,7-dioxo-6-pyridin-4-ylmethyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide;

 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-dimethoxy-benzylamide;

25 6-(4-Methanesulfonyl-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-dimethoxy-benzylamide;

 8-Methyl-5,7-dioxo-6-(4-sulfamoyl-benzyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-dimethoxy-benzylamide;

 6-(4-Dimethylsulfamoyl-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-dimethoxy-benzylamide;

30 8-Methyl-5,7-dioxo-6-pyridin-3-ylmethyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-dimethoxy-benzylamide;

8-Methyl-5,7-dioxo-6-pyridin-2-ylmethyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-dimethoxy-benzylamide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-methoxy-benzylamide;

5 6-(3-Methoxy-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-methoxy-benzylamide;

6-(3-Methoxy-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide;

10 6-Benzo[1,3]dioxol-5-ylmethyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methylsulfanyl-benzylamide;

15 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-dichlorobenzylamide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxybenzylamide;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide;

20 6-(4-Pyridylmethyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide hydrochloride;

6-(4-Chlorobenzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-dichlorobenzylamide;

25 6-(4-Chlorobenzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide;

6-(3,4-Dichlorobenzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide;

6-Benzoyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide;

30 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-fluoro-benzylamide;

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-
2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride;

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-
2-carboxylic acid biphenyl-4-ylamide;

5 6-Benzyl-8-formyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-
2-carboxylic acid 4-fluoro-benzylamide; and

6-Benzyl-8-hydroxymethyl-5,7-dioxo-6,7-dihydro-5H-
thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide.

Another invention embodiment is a compound of Formula VIII, or a
10 pharmaceutically acceptable salt thereof, selected from:

4-[2-(4-Methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-
c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester;

4-[2-(3-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-
c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester;

15 4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-
c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester;

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-
carboxylic acid benzyl ester;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-
20 2-carboxylic acid benzyl ester;

6-Benzyl-3-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-
2-carboxylic acid methyl ester;

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-
2-carboxylic acid methyl ester;

25 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-
2-carboxylic acid pyridin-4-ylmethyl ester;

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-
30 2-carboxylic acid pyridin-4-ylmethyl ester;

8-Methyl-5,7-dioxo-6-pyridin-4-ylmethyl-6,7-dihydro-5H-
thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzyl ester; and

6-Benzyl-3-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-
2-carboxylic acid benzyl ester.

Another invention embodiment is a compound of Formula I, or a pharmaceutically acceptable salt thereof, selected from:

6-Benzoyl-thiazolo[3,2-c]pyrimidine-5,7-dione;
6-(4-Chlorobenzyl)-thiazolo[3,2-c]pyrimidine-5,7-dione;
5 6-Pyridin-4-ylmethyl-thiazolo[3,2-c]pyrimidine-5,7-dione;
8-Methyl-thiazolo[3,2-c]pyrimidine-5,7-dione;
8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid;
10 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid;
4-(8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-yl-methyl)-benzoic acid tert-butyl ester; and
8-Methyl-6-[4-(Morpholine-4-sulfonyl)benzyl]-thiazolo[3,2-c]pyrimidine-5,7-dione.
15 Another invention embodiment is a compound of Formula III, or a pharmaceutically acceptable salt thereof, or a tautomer thereof, selected from:
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid prop-2-ynylamide;
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (piperidin-4-ylmethyl)-amide hydrochloride;
20 6-(4-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide;
6-(4-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide;
25 6-(4-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide;
6-(3-Bromo-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide;
30 6-(3-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide;
6-(3,4-Dichloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide;

6-(4-Bromo-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide;

6-(3-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide;

5 6-(3-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide;

6-(3,4-Dibromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide;

10 6-(4-Bromo-3-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide;

 6-(3,4-Difluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide;

15 6-(3-Bromo-4-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide;

 6-(3-Chloro-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide;

 6-(4-Chloro-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-amino-pyridin-4-ylmethyl)-amide;

20 6-(4-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide;

 6-(4-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide;

 6-(4-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide;

25 6-(3-Bromo-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide;

 6-(3-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide;

 6-(3,4-Dichloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide;

30 6-(4-Bromo-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide;

 6-(4-Bromo-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide;

6-(3-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide;

6-(3-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide;

5 6-(3,4-Dibromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide;

6-(4-Bromo-3-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide;

10 6-(3,4-Difluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide;

6-(3-Bromo-4-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide;

15 6-(3-Chloro-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide;

6-(4-Chloro-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-ethoxy-pyridin-4-ylmethyl)-amide;

20 6-(4-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-hydroxy-pyridin-3-ylmethyl)-amide;

6-(4-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-hydroxy-pyridin-3-ylmethyl)-amide;

25 6-(4-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-hydroxy-pyridin-3-ylmethyl)-amide;

6-(3-Bromo-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-hydroxy-pyridin-3-ylmethyl)-amide;

30 6-(3-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-hydroxy-pyridin-3-ylmethyl)-amide;

6-(3,4-Dichloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-hydroxy-pyridin-3-ylmethyl)-amide;

6-(4-Bromo-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-hydroxy-pyridin-3-ylmethyl)-amide;

6-(3-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-hydroxy-pyridin-3-ylmethyl)-amide;

6-(3-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-hydroxy-pyridin-3-ylmethyl)-amide;

5 6-(3,4-Dibromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-hydroxy-pyridin-3-ylmethyl)-amide;

6-(4-Bromo-3-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-hydroxy-pyridin-3-ylmethyl)-amide;

10 6-(3,4-Difluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-hydroxy-pyridin-3-ylmethyl)-amide;

6-(3-Bromo-4-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-hydroxy-pyridin-3-ylmethyl)-amide;

15 6-(3-Chloro-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-hydroxy-pyridin-3-ylmethyl)-amide;

6-(4-Chloro-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-hydroxy-pyridin-3-ylmethyl)-amide;

20 6-(4-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide;

6-(4-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide;

25 6-(4-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide;

6-(3-Bromo-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide;

30 6-(3-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide;

6-(3,4-Dichloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide;

6-(4-Bromo-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide;

5 6-(3-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide;

 6-(3-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide;

 6-(3,4-Dibromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide;

10 6-(4-Bromo-3-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide;

 6-(3,4-Difluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide;

15 6-(3-Bromo-4-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide;

 6-(3-Chloro-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide;

20 6-(4-Chloro-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide;

 6-(4-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-pyridin-4-ylmethyl)-amide;

25 6-(4-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-pyridin-4-ylmethyl)-amide;

 6-(4-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-pyridin-4-ylmethyl)-amide;

30 6-(3-Bromo-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-pyridin-4-ylmethyl)-amide;

6-(3-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-pyridin-4-ylmethyl)-amide;

6-(3,4-Dichloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-pyridin-4-ylmethyl)-amide;

5 6-(4-Bromo-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-pyridin-4-ylmethyl)-amide;

6-(3-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-pyridin-4-ylmethyl)-amide;

10 6-(3-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-pyridin-4-ylmethyl)-amide;

6-(3,4-Dibromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-pyridin-4-ylmethyl)-amide;

15 6-(4-Bromo-3-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-pyridin-4-ylmethyl)-amide;

6-(3,4-Difluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-pyridin-4-ylmethyl)-amide;

20 6-(3-Bromo-4-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-pyridin-4-ylmethyl)-amide;

6-(3-Chloro-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-pyridin-4-ylmethyl)-amide;

25 6-(4-Chloro-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-pyridin-4-ylmethyl)-amide;

6-(4-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide;

30 6-(4-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide;

6-(4-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide;

6-(3-Bromo-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide;

6-(3-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide;

6-(3,4-Dichloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide;

6-(4-Bromo-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide;

6-(3-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide;

6-(3-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide;

6-(3,4-Dibromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide;

6-(4-Bromo-3-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide;

6-(3,4-Difluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide;

6-(3-Chloro-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide;

6-(4-Chloro-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide;

6-(4-Chloro-3-bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methylamino-pyridin-4-ylmethyl)-amide;

6-(4-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide;

6-(4-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide;

6-(4-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide;

5 6-(3-Bromo-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide;

6-(3-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide;

10 6-(3,4-Dichloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide;

6-(4-Bromo-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide;

15 6-(3-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide;

6-(3-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide;

20 6-(3,4-Dibromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide;

6-(4-Bromo-3-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide;

25 6-(3,4-Difluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide;

6-(3-Bromo-4-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide;

6-(3-Chloro-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide;

30 6-(4-Chloro-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide;

6-(4-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide;

6-(4-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide;

6-(4-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide;
6-(3-Bromo-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide;
5 6-(3-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide;
6-(3,4-Dichloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide;
10 6-(4-Bromo-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide;
6-(3-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide;
15 6-(3-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide;
6-(3,4-Dibromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide;
6-(4-Bromo-3-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide;
20 6-(3,4-Difluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide;
6-(3-Bromo-4-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide;
6-(3-Chloro-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide;
25 6-(4-Chloro-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-amino-pyridin-3-ylmethyl)-amide;
6-(4-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide;
30 6-(4-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide;
6-(4-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide;

6-(3-Bromo-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide;
6-(3-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide;
6-(3,4-Dichloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide;
6-(4-Bromo-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide;
6-(3-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide;
6-(3-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide;
6-(3,4-Dibromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide;
6-(4-Bromo-3-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide;
6-(3,4-Difluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide;
6-(3-Bromo-4-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide;
6-(3-Chloro-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide;
6-(4-Chloro-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-ethoxy-pyridin-3-ylmethyl)-amide;
6-(4-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;
6-(4-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;
6-(4-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;
6-(3-Bromo-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;

6-(3-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;

6-(3,4-Dichloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;

5 6-(4-Bromo-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;

10 6-(3-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;

15 6-(3-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;

20 6-(3,4-Dibromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;

25 6-(4-Bromo-3-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;

30 6-(3,4-Difluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;

35 6-(3-Bromo-4-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;

40 6-(3-Chloro-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;

45 6-(4-Chloro-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide;

50 6-(4-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;

55 6-(4-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;

60 6-(4-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;

6-(3-Bromo-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;

6-(3-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;

6-(3,4-Dichloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;

6-(4-Bromo-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;

6-(3-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;

6-(3-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;

6-(3,4-Dibromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;

6-(4-Bromo-3-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;

6-(3,4-Difluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;

6-(3-Bromo-4-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;

6-(3-Chloro-4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;

6-(4-Chloro-3-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-3-ylmethyl)-amide;

6-(4-Cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide; and

6-(4-Isopropylsulfamoyl-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide.

Another invention embodiment is a compound of Formula I, selected
5 from:

8-Methyl-5,7-dioxo-6-(3-oxo-3-phenyl-propyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide;

8-Methyl-6-(1-phenylethyl) 5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluorobenzylamide;

10 8-Methyl-5,7-dioxo-6-(2-phenylmethanesulfonyl-ethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluorobenzylamide;

6-(5-Cyano-pentyl)-8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluorobenzylamide;

15 6-(E)-But-2-enyl-8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluorobenzylamide;

8-Methyl-5,7-dioxo-6-(E)-pent-2-enyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluorobenzylamide;

6-sec-Butyl-8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluorobenzylamide;

20 8-Methyl-6-(2-methyl-allyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluorobenzylamide;

6-(1-Ethyl-propyl)-8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluorobenzylamide;

25 8-Methyl-5,7-dioxo-6-pent-2-ynyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluorobenzylamide;

6-(2-Benzensulfonyl-ethyl)-8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluorobenzylamide;

8-Methyl-6-(3-methyl-but-2-enyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluorobenzylamide;

30 6-[2-(4-Fluoro-benzensulfonyl)-ethyl]-8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluorobenzylamide;

6-[3-(4-Fluoro-phenyl)-3-oxo-propyl]-8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluorobenzylamide;

8-Methyl-5,7-dioxo-6-{2-[(1-phenyl-methanoyl)-amino]-ethyl}-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluorobenzylamide;

8-Methyl-5,7-dioxo-6-(2-phenoxy-ethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluorobenzylamide; and

5 {5-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidine-6-ylmethyl]-isoxazol-3-yl} -carbamic acid methyl ester.

A further embodiment of this invention is use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by an MMP-13 enzyme.

10 Another invention embodiment is use of a compound of Formulas II, III, IV, V, VI, VII, or VIII, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by an MMP-13 enzyme.

15 Another invention embodiment is use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer.

Another invention embodiment is use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of rheumatoid arthritis.

20 Another invention embodiment is use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of osteoarthritis.

25 Another invention embodiment is use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of heart failure.

Another invention embodiment is use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of inflammation.

30 A further embodiment of this invention is a pharmaceutical composition, comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, admixed with a carrier, excipient, or diluent.

Another invention embodiment are compositions that comprise compounds of Formulas II, III, IV, V, VI, VII, or VIII, or a pharmaceutically acceptable salt thereof.

5 Another embodiment of this invention is a method for inhibiting MMP-13 in an animal, comprising administering to the animal an MMP-13 inhibiting amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

10 A further embodiment is a method for treating a disease mediated by an MMP-13 enzyme, comprising administering to a patient suffering from such a disease an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

15 Another invention embodiment is a method of treating cancer, comprising administering to a patient suffering from such a disease an anticancer effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Another invention embodiment is a method of treating breast carcinoma, comprising administering to a patient suffering from such a disease an anticancer effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

20 Another invention embodiment is a method of treating inflammation, comprising administering to a patient suffering from such a disease an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

25 Another invention embodiment is a method of treating heart failure, comprising administering to a patient suffering from such a disease an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

30 Another invention embodiment is a method of treating rheumatoid arthritis, comprising administering to a patient suffering from such a disease an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Another invention embodiment is a method of treating osteoarthritis, comprising administering to a patient suffering from such a disease an effective

C(=O)N(R⁵)-(CH₂)_m aryl, C(=O)N(R⁵)-(CH₂)_m substituted aryl, C(=O)N(R⁵)-(CH₂)_m heteroaryl, C(=O)N(R⁵)-(CH₂)_m substituted heteroaryl, C≡C-(CH₂)_m aryl, C≡C-(CH₂)_m substituted aryl, C≡C-(CH₂)_m-heteroaryl, C≡C-(CH₂)_m substituted heteroaryl, C≡C-(CH₂)_m carbocycle, C≡C-(CH₂)_m substituted carbocycle, (CH₂)_m-O-aryl, (CH₂)_m-O-substituted aryl, (CH₂)_m COR⁵, (CH₂)_m CONR⁵R⁶

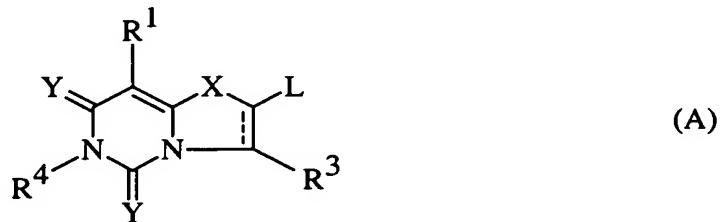
NH
||
(CH₂)_m CNR⁵R⁶,

S
||
(CH₂)_m CNR⁵R⁶, or (CH₂)_m CO₂R⁵; m is an integer from 0 to 6;

R⁵ and R⁶ independently are hydrogen, C₁-C₆ alkyl, substituted C₁-C₆ alkyl,
(CH₂)_m aryl, (CH₂)_m substituted aryl, (CH₂)_m heteroaryl or (CH₂)_m substituted heteroaryl, or R⁵ and R⁶ are taken together with the nitrogen atom to which they are attached complete a 3- to 7-membered ring containing carbon atoms, the nitrogen atom bearing R⁵ and R⁶, and optionally 1 or 2 heteroatoms independently selected from O, S, and NR², wherein R² is as defined above; and

n is 0 or 1; with the proviso that R² and R⁴ are not both selected from hydrogen and C₁-C₆ alkyl,

the process comprising the step of:
contacting a compound of Formula (A)



wherein X, Y, R¹, R³ and R⁴ are as defined above; and

L is a group K or Q, wherein

K is halo, $B(OH)_2$, $Sn(C_1-C_6\text{ alkyl})_3$, or $OS(O)_2CF_3$, and

Q is CO_2H , CO_2M , $C(=O)\text{-halo}$, $C(=O)\text{-OR}^7$, $C(=O)NR^8R^9$,

$C(=O)\text{-C(halo)}_3$, or $C\equiv N$,

5 wherein R^7 is pentafluorophenyl, $C(=O)R^4$, wherein R^4 is as defined above, or $S(O)_2R^4$, wherein R^4 is as defined above;

10 R^8 and R^9 are taken together with the nitrogen atom to which they are attached to form imidazol-1-yl, phthalimid-1-yl, benzotriazol-1-yl, or tetrazol-1-yl; and M is an alkali earth metal cation or alkaline earth metal cation;

with a solvent and, when L is the group Q, a compound of Formula (B)



wherein R^3 is as defined above and D is HO , $HN(R^5)$, MO , or $MN(R^5)$;

wherein R^5 and M are as defined above;

15 optionally in the presence of from 1 to 3 agents selected from:

a coupling agent, a tertiary organic amine, an acid catalyst, a base catalyst, an acid halide, and an acid anhydride.

Another invention embodiment is the above process comprising the step

20 of:

contacting a compound of Formula (A)

as defined above with a solvent and, when

L is the group K, a compound of Formula (C)



25 wherein R^3 is as defined above and

G is hydrogen or halo;

optionally in the presence of a coupling catalyst.

Another invention embodiment is any invention process wherein Y is O and X is S.

Another invention embodiment is any invention process wherein Y is O, X is S, and R³ is C₂-C₁₀ alkynyl.

Another invention embodiment is any invention process wherein R³ is (CO₂)_n(CH₂)_maryl, (CO₂)_n(CH₂)_m substituted aryl, (CO₂)_n(CH₂)_m heteroaryl, or (CO₂)_n(CH₂)_m substituted heteroaryl, wherein n and m are as defined above, 5 Y is O, and X is S.

Another invention embodiment is any invention process wherein R³ is C(=O)N(R⁵)(CH₂)_m aryl, C(=O)N(R⁵)(CH₂)_m substituted aryl, 10 C(=O)N(R⁵)(CH₂)_m heteroaryl, or C(=O)N(R⁵)(CH₂)_m substituted heteroaryl, Y is O, and X is S.

Another invention embodiment is any invention process wherein L is CO₂H, CO₂M, or C(=O)-halo.

Another invention embodiment is any invention process wherein L is halo.

Another invention embodiment is any invention process wherein G is H.

15

DETAILED DESCRIPTION OF THE INVENTION

The compounds provided by this invention are those defined by Formula I. In Formula I, R¹ to R⁴ include "C₁-C₆ alkyl" groups. These are straight and branched carbon chains having from 1 to 6 carbon atoms. Examples of such alkyl groups include methyl, ethyl, isopropyl, tert-butyl, neopentyl, and n-hexyl. The 20 alkyl groups can be substituted if desired, for instance with groups such as hydroxy, amino, alkyl, and dialkylamino, halo, trifluoromethyl, carboxy, nitro, and cyano.

Examples of NR⁴R⁵ groups include amino, methylamino, di-isopropylamino, acetyl amino, propionyl amino, 3-aminopropyl amino, 25 3-ethylaminobutyl amino, 3-di-n-propylamino-propyl amino, 4-diethylaminobutyl amino, and 3-carboxypropionyl amino. R⁴ and R⁵ can be taken together with the nitrogen to which they are attached to form a ring having 3 to 7 carbon atoms and 1, 2, or 3 heteroatoms selected from the group consisting of nitrogen, substituted

nitrogen, oxygen, and sulfur. Examples of such cyclic NR⁴R⁵ groups include pyrrolidinyl, piperazinyl, 4-methylpiperazinyl, 4-benzylpiperazinyl, pyridinyl, piperidinyl, pyrazinyl, morpholinyl, and the like.

“Halo” includes fluoro, chloro, bromo, and iodo. It should be appreciated
5 that invention compounds do not include compounds containing an N-halo group.

“Alkenyl” means straight and branched hydrocarbon radicals having from
2 to 6 carbon atoms and one double bond and includes ethenyl, 3-buten-1-yl,
2-ethenylbutyl, 3-hexen-1-yl, and the like.

“Alkynyl” means straight and branched hydrocarbon radicals having from
10 2 to 10 carbon atoms and one triple bond and includes ethynyl, 3-butyn-1-yl,
propynyl, 2-butyn-1-yl, 3-pentyn-1-yl, 1-hexyn-1-yl, 7,7-dimethyl-1-octyn-1-yl,
and the like.

“Cycloalkyl” means a monocyclic or polycyclic hydrocarbyl group such as
cyclopropyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclobutyl, adamantyl,
15 norpinanyl, decalinyl, norbornyl, cyclohexyl, and cyclopentyl. Such groups can be
substituted with groups such as hydroxy, keto, and the like. Examples of
substituted cycloalkyl include 4-carboxycyclohexyl, 4-oxo-cyclohexyl,
4-(carboxymethyl)-cyclobutyl, 3-methyl-cyclopentyl, and
3-(carboxymethyl)cyclopentyl. Also included are rings in which 1 to
20 3 heteroatoms replace carbons. Such groups are termed “heterocycle” or
“heterocyclyl”, which mean a cycloalkyl group also bearing at least one
heteroatom selected from O, S, or NR², examples being oxiranyl, pyrrolidinyl,
4-methylpiperazinyl, piperidyl, tetrahydropyranyl, and morpholinyl. The group R²
here is as defined above for Formula I, except where R² contains the functional
25 group “NR⁵R⁶”, the groups R⁵ and R⁶ are not taken together with the nitrogen
atom to which they are attached to complete a 3- to 7-membered ring.

“Alkoxy” refers to the alkyl groups mentioned above bound through
oxygen, examples of which include methoxy, ethoxy, isopropoxy, tert-butoxy, and
the like. In addition, alkoxy refers to polyethers such as -O-(CH₂)₂-O-CH₃, and
30 the like.

“Alkanoyl” groups are alkyl linked through a carbonyl, i.e., C₁-C₅-C(O)-.
Such groups include formyl, acetyl, propionyl, butyryl, and isobutyryl.

"Acyl" means an alkyl or aryl (Ar) group bonded through a carbonyl group, i.e., R-C(O)-. For example, acyl includes a C₁-C₆ alkanoyl, including substituted alkanoyl, wherein the alkyl portion can be substituted by NR⁴R⁵ or a carboxylic or heterocyclic group. Typical acyl groups include acetyl, benzoyl, and the like.

5

The alkyl, alkenyl, alkoxy, and alkynyl groups described above are optionally substituted, preferably by 1 to 3 groups selected from NR⁴R⁵, phenyl, substituted phenyl, heteroaryl, substituted heteroaryl, heterocycle, thio C₁-C₆ alkyl, C₁-C₆ alkoxy, hydroxy, carboxy, C₁-C₆ alkoxy carbonyl, halo, nitrile, cycloalkyl, and a 5- or 6-membered carbocyclic ring or heterocyclic ring having 1 or 2 heteroatoms selected from nitrogen, substituted nitrogen, oxygen, and sulfur. "Substituted nitrogen" means nitrogen bearing C₁-C₆ alkyl or (CH₂)_nPh where n is 1, 2, or 3. Perhalo and polyhalo substitution is also embraced.

10

Examples of substituted alkyl groups include 2-aminoethyl, pentachloroethyl, trifluoromethyl, 2-diethylaminoethyl, 2-dimethylaminopropyl, ethoxycarbonylmethyl, 3-phenylbutyl, methanylsulfanylmethyl, methoxymethyl, 3-hydroxypentyl, 2-carboxybutyl, 4-chlorobutyl, 3-cyclopropylpropyl, pentafluoroethyl, benzyl(B_n), 3-morpholinopropyl, piperazinylmethyl, pyridyl-20 4-methyl(Py-4-me), 3-(pyridyl-4-thio)propyl, and 2-(4-methylpiperazinyl)ethyl.

15

Examples of substituted alkynyl groups include 2-methoxyethynyl, 2-ethylsulfanyethynyl, 4-(1-piperazinyl)-3-(butynyl), 3-phenyl-5-hexynyl, 3-diethylamino-3-butynyl, 4-chloro-3-butynyl, 4-cyclobutyl-4-hexenyl, and the like.

20

Typical substituted alkoxy groups include aminomethoxy, trifluoromethoxy, 2-diethylaminoethoxy, 2-ethoxycarbonylethoxy, 3-hydroxypropoxy, 6-carboxhexyloxy, and the like.

25

Further, examples of substituted alkyl, alkenyl, and alkynyl groups include dimethylaminomethyl, carboxymethyl, 4-dimethylamino-3-buten-1-yl, 5-ethylmethylamino-3-pentyn-1-yl, 3-(3-methoxyphenyl)-propyn-1-yl, 3-(3,4-difluorophenyl)-propyn-1-yl, 4-morpholinobutyl, 4-tetrahydropyrinidylbutyl,

30

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3-imidazolidin-1-ylpropyl, 4-tetrahydrothiazol-3-yl-butyl, phenylmethyl, 3-chlorophenylmethyl, and the like.

The terms "Ar" and "aryl" refer to unsubstituted and substituted aromatic groups. Heteroaryl groups have from 4 to 10 ring atoms, from 1 to 4 of which are independently selected from the group consisting of O, S, and N. Preferred heteroaryl groups have 1 or 2 heteroatoms in a 5- or 6-membered aromatic ring. Mono- and bicyclic aromatic ring systems are included in the definition of aryl and heteroaryl. Typical aryl groups include phenyl and naphthyl. Typical substituted aryl groups include 3,4-difluorophenyl, 4-carboxyphenyl, 3,4-methylenedioxophenyl, 4-carboxymethylphenyl, 3-methoxyphenyl, and 7-fluoro-1-naphthyl. Typical heteroaryl groups include pyridyl, thienyl, benzothienyl, indolyl, furanyl, thiazolyl, isothiazolyl, indazolyl, 2-oxo-2H-1-benzopyranyl, and imidazolyl. Typical substituted heteroaryl groups include 3-methoxy-isothiazolyl, 3-methoxypyridin-4-yl, 4-ethylbenzothienyl, 4-thiopyridyl, 2-methoxy-pyridin-4-yl, 1-methylpyrazol-4-yl, and 2-methyl-pyridin-3-yl.

Preferred Ar groups are phenyl and phenyl substituted by 1, 2, or 3 groups independently selected from alkyl, alkoxy, alkoxy carbonyl, thio, thioalkyl, (C_1 - C_6 alkyl)sulfanyl, (C_1 - C_6 alkyl)sulfonyl, halo, hydroxy, $(CH_2)_{0-6}CO_2R^7$, trifluoromethyl, trifluoromethoxy, nitro, amino of the formula $-NR^4R^5$, $C(=O)NR^5R^6$, $N(R^4)C(=O)OR^5$, and $T(CH_2)_mQR^4$ or $T(CH_2)_mCO_2R^4$, wherein m is 1 to 6, T is O, S, NR^4 , $N(O)R^4$, NR^4R^6Y , or CR^4R^5 , Q is O, S, NR^5 , $N(O)R^5$, or NR^5R^6Y , wherein R^4-R^6 are as described above, and R^7 is hydrogen, alkyl, or substituted alkyl, for example, methyl, trichloroethyl, diphenylmethyl, and the like. The alkyl and alkoxy groups can be substituted as defined above. For example, typical groups are carboxyalkyl, alkoxy carbonylalkyl, hydroxyalkyl, hydroxyalkoxy, and alkoxyalkyl. Examples of substituted phenyl are 3-methoxyphenyl, 2,6-dichlorophenyl, 3-nitrophenyl, 4-dimethylaminophenyl, and biphenyl.

Preferred heteroaryl groups include thienyl, furanyl, pyrrolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,2,4-triazolyl, tetrazolyl, benzofuranyl, benzothienyl, indolyl,

benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, pyridinyl, pyrimidinyl, quinolinyl, isoquinolinyl, and 2-oxo-2H-1-benzopyranyl.

Preferred heteroaryl groups may be substituted on a carbon atom as described above for substituted phenyl, and may further be substituted on a ring nitrogen atom (i.e., by replacing a hydrogen from a ring nitrogen atom, which is an NH group) with (C₁-C₆ alkyl) C(=O), C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₁₀ alkynyl, or benzyl.

The term "substituted", unless otherwise defined, includes from 1 to 3 substituents selected from:

10 C₁-C₆ alkyl; C₂-C₆ alkenyl; C₂-C₆ alkynyl; C₁-C₆ alkoxy; phenyl; (C₁-C₆ alkoxy)carbonyl; (C₁-C₆ alkyl)sulfanyl; (C₁-C₆ alkyl)carbonyl; OH; NH₂; N(H)R⁴, wherein R⁴ is as defined above for Formula I; NR⁴R⁵, wherein R⁴ and R⁵ are as defined above for Formula I, or R⁴ and R⁵ are taken together with the nitrogen atom to which they are attached to form a 3- to 7-membered saturated ring containing carbon atoms and optionally from 1 or 2 heteroatoms selected from O, S, S(O), S(O)₂, N(H), and N(C₁-C₆ alkyl), wherein the ring may be optionally substituted on a carbon atom with 1 oxo (i.e., =O) group;

15 C(=O)NR⁴R⁵, wherein R⁴ and R⁵ are as defined immediately above, or R⁴ and R⁵ are taken together with the nitrogen atom to which they are attached to form a 3- to 7-membered saturated ring containing carbon atoms and optionally 1 or 2 heteroatoms selected from O, S, S(O), S(O)₂, N(H), and N(C₁-C₆ alkyl), wherein the ring may be optionally substituted on a carbon atom with 1 oxo (i.e., =O) group;

20 CN; NO₂; CF₃; CO₂H; CHO; SH; (C₁-C₆alkyl) S(O); (C₁-C₆ alkyl)sulfonyl; halo; S(O)₂NR⁴R⁵, wherein R⁴ and R⁵ are as defined above for Formula I, or R⁴ and R⁵ are taken together with the nitrogen atom to which they are attached to form a 3- to 7-membered saturated ring containing carbon atoms and optionally 1 or 2 heteroatoms selected from O, S, S(O), S(O)₂, N(H), and N(C₁-C₆ alkyl), wherein the ring may be optionally substituted on a carbon atom with 1 oxo (i.e., =O) group;

25 CN; NO₂; CF₃; CO₂H; CHO; SH; (C₁-C₆alkyl) S(O); (C₁-C₆ alkyl)sulfonyl; halo; S(O)₂NR⁴R⁵, wherein R⁴ and R⁵ are as defined above for Formula I, or R⁴ and R⁵ are taken together with the nitrogen atom to which they are attached to form a 3- to 7-membered saturated ring containing carbon atoms and optionally 1 or 2 heteroatoms selected from O, S, S(O), S(O)₂, N(H), and N(C₁-C₆ alkyl), wherein the ring may be optionally substituted on a carbon atom with 1 oxo (i.e., =O) group;

30 CN; NO₂; CF₃; CO₂H; CHO; SH; (C₁-C₆alkyl) S(O); (C₁-C₆ alkyl)sulfonyl; halo; S(O)₂NR⁴R⁵, wherein R⁴ and R⁵ are as defined above for Formula I, or R⁴ and R⁵ are taken together with the nitrogen atom to which they are attached to form a 3- to 7-membered saturated ring containing carbon atoms and optionally 1 or 2 heteroatoms selected from O, S, S(O), S(O)₂, N(H), and N(C₁-C₆ alkyl), wherein the ring may be optionally substituted on a carbon atom with 1 oxo (i.e., =O) group;

ring may be optionally substituted on a carbon atom with 1 oxo (i.e., =O) group;

OCF₃; and (CH₂)_mCO₂H, wherein m is as defined above for Formula I.

The phrase "tertiary organic amine" means a trisubstituted nitrogen group
5 wherein the 3 substituents are independently selected from C₁-C₁₂ alkyl,
C₃-C₁₂ cycloalkyl, benzyl, or wherein two of the substituents are taken together
with the nitrogen atom to which they are attached to form a 5- or 6-membered,
monocyclic heterocycle containing one nitrogen atom and carbon atoms, and the
third substituent is selected from C₁-C₁₂ alkyl and benzyl, or wherein the three
10 substituents are taken together with the nitrogen atom to which they are attached
to form a 7- to 12-membered bicyclic heterocycle containing 1 or 2 nitrogen
atoms and carbon atoms, and optionally a C=N double bond when 2 nitrogen
atoms are present. Illustrative examples of tertiary organic amine include
triethylamine, diisopropylethylamine, benzyl diethylamino, dicyclohexylmethyl-
15 amine, 1,8-diazabicycle[5.4.0]undec-7-ene ("DBU"),
1,4-diazabicyclo[2.2.2]octane ("TED"), and 1,5-diazabicycle[4.3.0]non-5-ene.

The term "coupling agent" includes any reagent, or any combination of
two, three, or four reagents, conventionally used to promote coupling of a
carboxylic acid, or a pharmaceutically acceptable salt thereof, with an alcohol or
20 an amine to yield a carboxylic ester or carboxylic amide, respectively. The
coupling agents are described in *Reagents for Organic Synthesis*, by Fieser and
Fieser, John Wiley & Sons, Inc., New York, 2000; *Comprehensive Organic
Transformations*, by Richard C. Larock, VCH Publishers, Inc., New York, 1989;
the series *Compendium of Organic Synthetic Methods* (1989) by Wiley-
25 Interscience; and the text *Advanced Organic Chemistry*, 5th edition, by Jerry
March, Wiley-Interscience, New York (2001). Illustrative examples of coupling
agents include N,N'-carbonyldiimidazole ("CDI"), N, N'-
dicyclohexylcarbodiimide ("DCC"), triphenylphosphine with
diethylazodicarboxylate, bis(2-oxo-3-oxazolidinyl)phosphinic chloride ("BOP-
30 Cl"), POCl₃, Ti(Cl)₄, and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
hydrochloride ("EDAC").

The phrase "acid catalyst" means any protic or Lewis acid that is conventionally used to catalyze coupling of a carboxylic acid, or a pharmaceutically acceptable salt thereof, a nitrile, carboxylic ester, carboxylic amide, carboxylic acid halide, or carboxylic acid anhydride with an alcohol or an amine to yield a carboxylic ester or carboxylic amide, respectively. The acid catalysts are described in *Reagents for Organic Synthesis*, by Fieser and Fieser, John Wiley & Sons, Inc., New York, 2000; *Comprehensive Organic Transformations*, by Richard C. Larock, VCH Publishers, Inc., New York, 1989; the series *Compendium of Organic Synthetic Methods* (1989) by Wiley-Interscience; and the text *Advanced Organic Chemistry*, 5th edition, by Jerry March, Wiley-Interscience, New York (2001). Illustrative examples include anhydrous hydrogen chloride, hydrochloric acid, hydrogen bromide in acetic acid, zinc chloride, titanium tetrachloride, acetic acid, trifluoroacetic acid, phenol, sulfuric acid, methanesulfonic acid, magnesium sulfate, Amberlyst-15 resin, silica gel, and the like.

It should be appreciated that a nitrile may be contacted with an alcohol or an amine in the presence of an acid catalyst, and the resulting intermediate imidate or amidine, respectively, may be contacted with water to yield the carboxylic ester or carboxylic amide, respectively.

The phrase "base catalyst" means any base that is conventionally used to catalyze coupling of a carboxylic acid, or a pharmaceutically acceptable salt thereof, carboxylic ester, carboxylic amide, carboxylic acid halide, or carboxylic acid anhydride with an alcohol or an amine to yield a carboxylic ester or carboxylic amide, respectively. The base catalysts are described in *Reagents for Organic Synthesis*, by Fieser and Fieser, John Wiley & Sons, Inc., New York, 2000; *Comprehensive Organic Transformations*, by Richard C. Larock, VCH Publishers, Inc., New York, 1989; the series *Compendium of Organic Synthetic Methods* (1989) by Wiley-Interscience; and the text *Advanced Organic Chemistry*, 5th edition, by Jerry March, Wiley-Interscience, New York (2001). Illustrative examples include sodium hydroxide, sodium hydride, potassium tert-butoxide, a tertiary organic amine, titanium tetraisopropoxide, sodium methoxide, sodium acetate, sodium bicarbonate, potassium carbonate, basic alumina, and the like.

The phrase "acid halide" means any carboxylic acid halide or sulfonic acid halide that is conventionally used to catalyze coupling of a carboxylic acid, or a pharmaceutically acceptable salt thereof, with an alcohol or an amine to yield a carboxylic ester or carboxylic amide, respectively. The acid halides are described
5 in *Reagents for Organic Synthesis*, by Fieser and Fieser, John Wiley & Sons, Inc., New York, 2000; *Comprehensive Organic Transformations*, by Richard C. Larock, VCH Publishers, Inc., New York, 1989; the series *Compendium of
10 Organic Synthetic Methods* (1989) by Wiley-Interscience; and the text *Advanced Organic Chemistry*, 5th edition, by Jerry March, Wiley-Interscience, New York (2001). Illustrative examples include acetyl chloride, trifluoromethanesulfonyl chloride, 2,2-dimethylacetyl bromide, para-toluenesulfonyl chloride, pentafluoro-benzoyl chloride, and the like.

The phrase "acid anhydride" means any carboxylic acid anhydride or sulfonic acid anhydride that is conventionally used to catalyze coupling of a carboxylic acid, or a pharmaceutically acceptable salt thereof, with an alcohol or an amine to yield a carboxylic ester or carboxylic amide, respectively. The acid anhydrides are described in *Reagents for Organic Synthesis*, by Fieser and Fieser, John Wiley & Sons, Inc., New York, 2000; *Comprehensive Organic Transformations*, by Richard C. Larock, VCH Publishers, Inc., New York, 1989;
15 the series *Compendium of Organic Synthetic Methods* (1989) by Wiley-Interscience; and the text *Advanced Organic Chemistry*, 5th edition, by Jerry March, Wiley-Interscience, New York (2001). Illustrative examples include acetic anhydride, trifluoroacetic anhydride, trifluoromethanesulfonic acid anhydride, pentafluoro-benzoic anhydride, mixed anhydrides like
20 trifluoroacetyloxycarbonylmethyl, and the like.

The term "halide" includes fluoride, chloride, bromide, and iodide.

The phrase "coupling catalyst" means any metal catalyst, preferably a transition metal catalyst, that is conventionally used to catalyze coupling of an aryl halide, aryl trifluoromethanesulfonate, heteroaryl halide, or heteroaryl trifluoromethanesulfonate, or activated derivatives thereof, including arylboronic acids, heteroarylboronic acids, aryl stannanes, heteroarylstannanes, aryl magnesium halides, heteroaryl magnesium halides, aryl lithiums, or heteroaryl

lithiums, with an terminal alkyne to yield an arylalkyne or heteroarylalkyne. The coupling catalysts are described in *Reagents for Organic Synthesis*, by Fieser and Fieser, John Wiley & Sons, Inc., New York, 2000; *Comprehensive Organic Transformations*, by Richard C. Larock, VCH Publishers, Inc., New York, 1989; the series *Compendium of Organic Synthetic Methods* (1989) by Wiley-Interscience; and the text *Advanced Organic Chemistry*, 5th edition, by Jerry March, Wiley-Interscience, New York (2001). Illustrative examples of coupling catalysts include tetrakis(triphenylphosphine)palladium (0), palladium (II) chloride, palladium (II) acetate, iron (III) chloride, Heck reaction catalysts, Suzuki reaction catalysts, Stille reaction catalysts, and the like.

The term "patient" means a mammal. Preferred patients include humans, cats, dogs, cows, horses, pigs, and sheep.

The term "animal" means a mammal. Preferred animals are include humans, rats, mice, guinea pigs, rabbits, monkeys, cats, dogs, cows, horses, pigs, and sheep.

The phrases "therapeutically effective amount" and "effective amount" are synonymous unless otherwise indicated, and mean an amount of a compound of the present invention that is sufficient to improve the condition, disease, or disorder being treated. Determination of a therapeutically effective amount, as well as other factors related to effective administration of a compound of the present invention to a patient in need of treatment, including dosage forms, routes of administration, and frequency of dosing, may depend upon the particulars of the condition that is encountered, including the patient and condition being treated, the severity of the condition in a particular patient, the particular compound being employed, the particular route of administration being employed, the frequency of dosing, and the particular formulation being employed. Determination of a therapeutically effective treatment regimen for a patient is within the level of ordinary skill in the medical or veterinarian arts.

The phrase "admixed" or "in admixture" means the ingredients so mixed comprise either a heterogeneous or homogeneous mixture. Preferred is a homogeneous mixture.

The phrases "pharmaceutical preparation" and "preparation" are synonymous unless otherwise indicated, and include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, 5 which is thus in association with it. Similarly, cachets and lozenges are included. Pharmaceutical preparations are fully described below.

The phrase "anticancer effective amount" means an amount of invention compound, or a pharmaceutically acceptable salt thereof, sufficient to inhibit, halt, or cause regression of the cancer being treated in a particular patient or patient 10 population. For example in humans or other mammals, an anticancer effective amount can be determined experimentally in a laboratory or clinical setting, or may be the amount required by the guidelines of the United States Food and Drug Administration, or equivalent foreign agency, for the particular cancer and patient being treated.

15 The phrase "anti-arthritis effective amount" means an amount of invention compound, or a pharmaceutically acceptable salt thereof, sufficient to inhibit, halt, or cause regression of the arthritis being treated in a particular patient or patient population. For example in humans or other mammals, an anti-arthritis effective amount can be determined experimentally in a laboratory or clinical setting, or 20 may be the amount required by the guidelines of the United States Food and Drug Administration, or equivalent foreign agency, for the particular arthritis and patient being treated.

The phrase "MMP-13 inhibiting amount" means an amount of invention compound, or a pharmaceutically acceptable salt thereof, sufficient to inhibit an 25 enzyme matrix metalloproteinase-13, including a truncated form thereof, including a catalytic domain thereof, in a particular animal or animal population. For example in a human or other mammal, an MMP-13 inhibiting amount can be determined experimentally in a laboratory or clinical setting, or may be the amount required by the guidelines of the United States Food and Drug 30 Administration, or equivalent foreign agency, for the particular MMP-13 enzyme and patient being treated.

It should be appreciated that the matrix metalloproteinases include the following enzymes:

MMP-1, also known as interstitial collagenase, collagenase-1, or fibroblast-type collagenase;

MMP-2, also known as gelatinase A or 72 kDa Type IV collagenase;

MMP-3, also known as stromelysin or stromelysin-1;

5 MMP-7, also known as matrilysin or PUMP-1;

MMP-8, also known as collagenase-2, neutrophil collagenase or polymorphonuclear-type ("PMN-type") collagenase;

MMP-9, also known as gelatinase B or 92 kDa Type IV collagenase;

10 MMP-10, also known as stromelysin-2;

MMP-11, also known as stromelysin-3;

MMP-12, also known as metalloelastase;

MMP-13, also known as collagenase-3;

MMP-14, also known as membrane-type ("MT") 1-MMP or MT1-MMP;

MMP-15, also known as MT2-MMP;

15 MMP-16, also known as MT3-MMP;

MMP-17, also known as MT4-MMP;

MMP-18; and

MMP-19.

Other known MMPs include MMP-26 (Matrilysin-2).

20 One aspect of the present invention is compounds that are selective inhibitors of the enzyme MMP-13. A selective inhibitor of MMP-13, as used in the present invention, is a compound that is ≥ 5 times more potent in vitro versus MMP-13, or a truncated form thereof, than versus at least one other matrix metalloproteinase enzyme such as, for example, MMP-1, MMP-2, MMP-3,

25 MMP-7, MMP-8, MMP-9, or MMP-14, or versus tumor necrosis factor alpha convertase ("TACE"). A preferred aspect of the present invention is compounds that are selective inhibitors of MMP-13 versus MMP-1.

Other aspects of the present invention are compounds of Formula I, or a pharmaceutically acceptable salt thereof, that are ≥ 10 , ≥ 20 , ≥ 50 , ≥ 100 , or ≥ 1000 times more potent versus MMP-13 than versus at least one of any other MMP 30 enzyme or TACE. Still other aspects of the present invention are compounds of Formula I, or a pharmaceutically acceptable salt thereof, that are selective

inhibitors of MMP-13 versus 2, 3, 4, 5, 6, or 7 other MMP enzymes, or versus TACE and 1, 2, 3, 4, 5, 6, or 7 other MMP enzymes.

It should be appreciated that the invention compounds of Formula I such as thiazolo[3,2-c]pyrimidines and oxazolo[3,2-c]pyrimidines that are only substituted with hydrogen or unsubstituted C₁-C₆ alkyl groups would not be potent or selective inhibitors of MMP-13, and are thus excluded from the compounds of the invention.

It should be appreciated that determination of proper dosage forms, dosage amounts, and routes of administration, is within the level of ordinary skill in the pharmaceutical and medical arts, and is described below.

The term "IC₅₀" means the concentration of test compound required to inhibit activity of a biological target, such as a receptor or enzyme, by 50%.

The phrase "catalytic domain" means the domain containing a catalytic zinc cation of the MMP enzyme, wherein the MMP enzyme contains two or more domains. A catalytic domain includes truncated forms thereof that retain at least some of the catalytic activity of MMP-13 or MMP-13CD. For example, the collagenases, of which MMP-13 is a member, have been reported to contain a signal peptide domain, a propeptide domain, a catalytic domain, and a hemopexin-like domain (Ye Qi-Zhuang, Hupe D., Johnson L., *Current Medicinal Chemistry*, 1996;3:407-418).

The phrase "a method for inhibiting MMP-13" includes methods of inhibiting full length MMP-13, truncated forms thereof that retain catalytic activity, including forms that contain the catalytic domain of MMP-13, as well as the catalytic domain of MMP-13 alone, and truncated forms of the catalytic domain of MMP-13 that retain at least some catalytic activity.

It should be appreciated that it has been shown previously (Ye Qi-Zhuang, et al., 1996, *supra*) that inhibitor activity against a catalytic domain of an MMP is predictive of the inhibitor activity against the respective full-length enzyme.

The compounds to be used in the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Some of the

invention compounds may have one or more chiral centers, and as such can exist as individual enantiomers and mixtures. This invention contemplates all racemic mixtures, pure enantiomers, as well as geometric and positional isomers.

The compounds of Formulas I to VIII are capable of further forming both
5 pharmaceutically acceptable formulations comprising salts, including but not limited to acid addition and/or base salts, solvents, and N-oxides of a compound of Formulas I to VIII. This invention also provides pharmaceutical formulations comprising a compound of Formulas I to VIII together with a pharmaceutically acceptable carrier, diluent, or excipient therefor. All of these forms can be used in
10 the method of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formulas I to VIII include nontoxic salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, phosphorus, and the like, as well as the salts derived from organic acids, such as aliphatic
15 mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate,
20 caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are the salts
25 of amino acids such as arginate, gluconate, galacturonate, and the like; see, for example, Berge et al., "Pharmaceutical Salts," *J. of Pharmaceutical Science*, 1977;66:1-19.

The acid addition salts of the basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting
30 the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metal hydroxides, or of organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, 5 chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine, and procaine; see, for example, Berge et al., *supra*.

The base addition salts of acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the 10 salt form with an acid and isolating the free acid in a conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

The compounds of the present invention can be formulated and 15 administered in a wide variety of oral and parenteral dosage forms, including transdermal and rectal administration. All that is required is that an MMP inhibitor be administered to a mammal suffering from a disease in an effective amount, which is that amount required to cause an improvement in the disease and/or the symptoms associated with such disease. It will be recognized to those skilled in 20 the art that the following dosage forms may comprise as the active component, a compound of Formula I or a corresponding pharmaceutically acceptable salt or solvate of a compound of Formula I.

A compound of Formula I, or a pharmaceutically acceptable salt thereof, 25 may be prepared by one of ordinary skill in the art of organic chemistry by procedures found in the chemical literature such as, for example, *Reagents for Organic Synthesis*, by Fieser and Fieser, John Wiley & Sons, Inc., New York, 2000; *Comprehensive Organic Transformations*, by Richard C. Larock, VCH Publishers, Inc., New York, 1989; the series *Compendium of Organic Synthetic Methods* (1989) by Wiley-Interscience; the text *Advanced Organic Chemistry*, 5th 30 edition, by Jerry March, Wiley-Interscience, New York (2001); or the *Handbook of Heterocyclic Chemistry*, by Alan R. Katritzky, Pergamon Press Ltd., London, (1985), to name a few. Alternatively, a skilled artisan may find methods useful for

preparing the invention compounds in the chemical literature by searching widely available databases such as, for example, those available from the *Chemical Abstracts Service*, Columbus, Ohio, or *MDL Information Systems GmbH* (formerly *Beilstein Information Systems GmbH*), Frankfurt, Germany.

5 Preparations of the compounds of the present invention may use starting materials, reagents, solvents, and catalysts that may be purchased from commercial sources or they may be readily prepared by adapting procedures in the references or resources cited above. Commercial sources of starting materials, reagents, solvents, and catalysts useful in preparing invention compounds include, 10 for example, *The Aldrich Chemical Company*, and other subsidiaries of Sigma-Aldrich Corporation, St. Louis, Missouri, *BACHEM*, *BACHEM A.G.*, Switzerland, or *Lancaster Synthesis Ltd.*, United Kingdom.

15 *Reagents for Organic Synthesis*, by Fieser and Fieser, John Wiley & Sons, Inc., New York, 2000; *Comprehensive Organic Transformations*, by Richard C. Larock, VCH Publishers, Inc., New York, 1989; the series *Compendium of Organic Synthetic Methods* (1989) by Wiley-Interscience; the text *Advanced Organic Chemistry*, 5th edition, by Jerry March, Wiley-Interscience, New York (2001); and the *Handbook of Heterocyclic Chemistry*, by Alan R. Katritzky, Pergamon Press Ltd., London, (1985) are hereby incorporated by reference.

20 The invention compounds are prepared by methods well-known to those skilled in the art of organic chemistry. The compounds of Formula I are prepared utilizing commercially available starting materials, or reactants that are readily prepared by standard organic synthetic techniques. A typical synthesis of the invention compounds of Formula I is shown in Scheme 1 below. The first step in 25 Scheme 1 comprises reacting a substituted (R^4) urea or thiourea (1) with a substituted or unsubstituted (R^1) malonic acid or ester (2) in the presence of acetic anhydride (with malonic acids) or alkali alkoxide (with malonic esters), respectively, to give a pyrimidinetrione (3). Reaction of the pyrimidinetrione (3) with phosphorus oxychloride at reflux for 1 to 2 hours gives the 30 chloropyrimidinedione (4). Reaction of the chloropyrimidinedione (4) with excess sodium hydrosulfide in dimethylformamide at 40°C to 45°C, followed by reaction with bromoacetaldehyde dimethylacetal at 40°C to 50°C gives a thio substituted

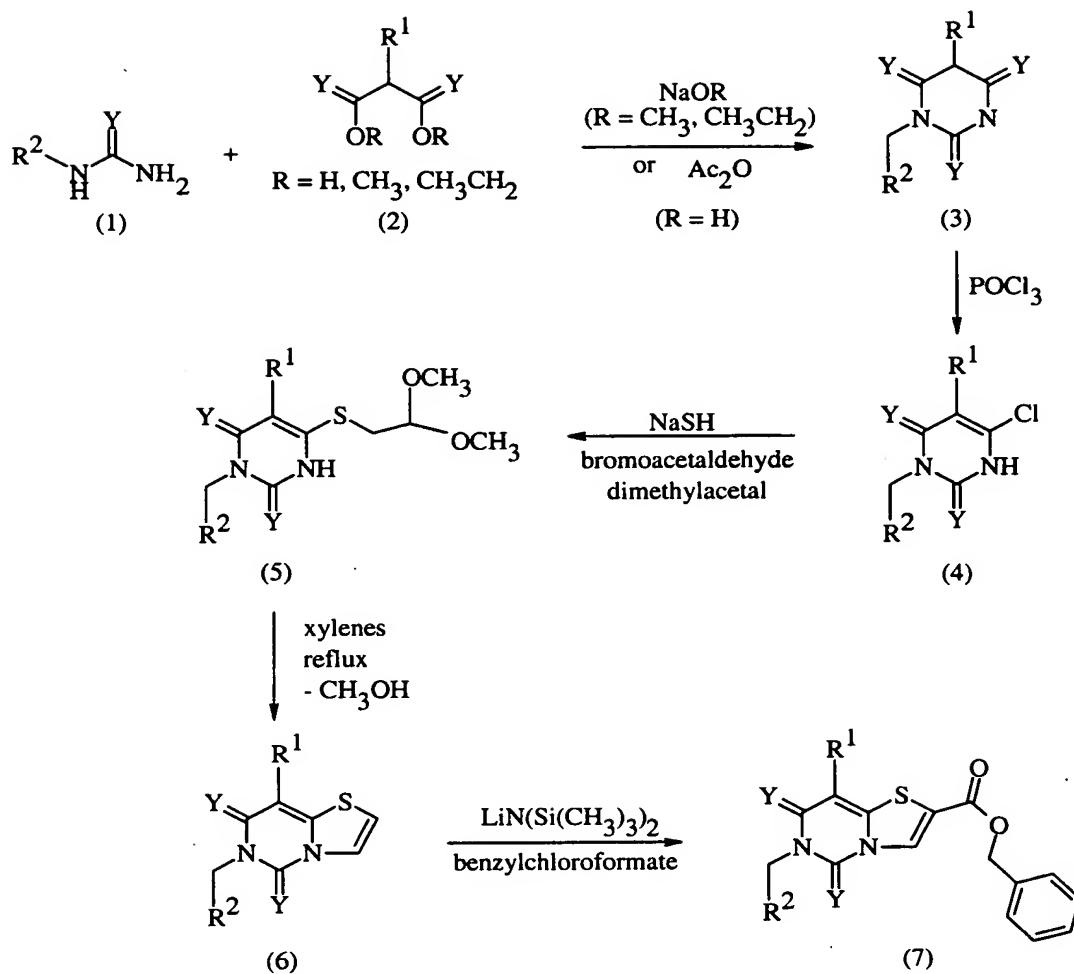
pyrimidinedione (5). Cyclization of the thio substituted pyrimidinedione (5) in the presence of catalytic para-toluenesulfonic acid in refluxing xylenes with azeotropic removal of methanol gives a thiazolopyrimidine of Formula I (6) (where R² and R³ both are H). Esters of structure (7) (Formula I where R² is 5 (CH₂)_m CO₂R⁵) are prepared by deprotonation of (6) with lithiumhexamethyldisilazane at -70°C to -80°C and reaction with chloroformates.

Amides or thioamides



10 (Formula I where R² is (CH₂)_m CNR⁵R⁶ or (CH₂)_m CNR⁵R⁶) are obtained by reaction of the lithiothiazolopyrimidines with isocyanates and isothiocyanates, respectively.

Scheme 1

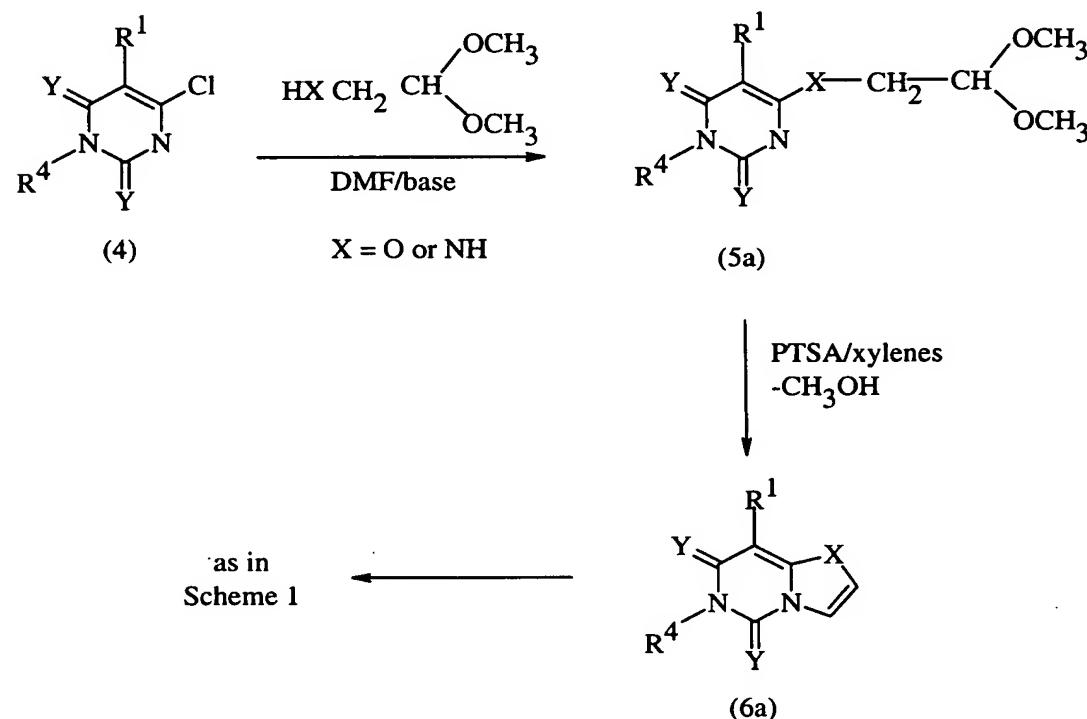


Invention compounds of Formula I, wherein X is O or NH, can be prepared according to essentially the same methodology described above for those compounds wherein X is S. The general process is illustrated in Scheme 1a. The chloropyrimidinedione (4) is reacted with a 2-hydroxyacetaldehyde dimethylacetal (for invention compounds where X is O), or with a 2-aminoacetaldehyde dimethylacetal (for invention compounds where X is NH). These reactions are carried out in an organic solvent such as dimethylformamide, and in the presence of a base such as sodium hydride or triethylamine to give the corresponding ether acetal (X = O) or amine acetal (X = NH), (Compound 5a). The ether acetals and amine acetals readily undergo cyclization by reaction with para-toluenesulfonic acid in refluxing xylenes (with azeotropic removal of

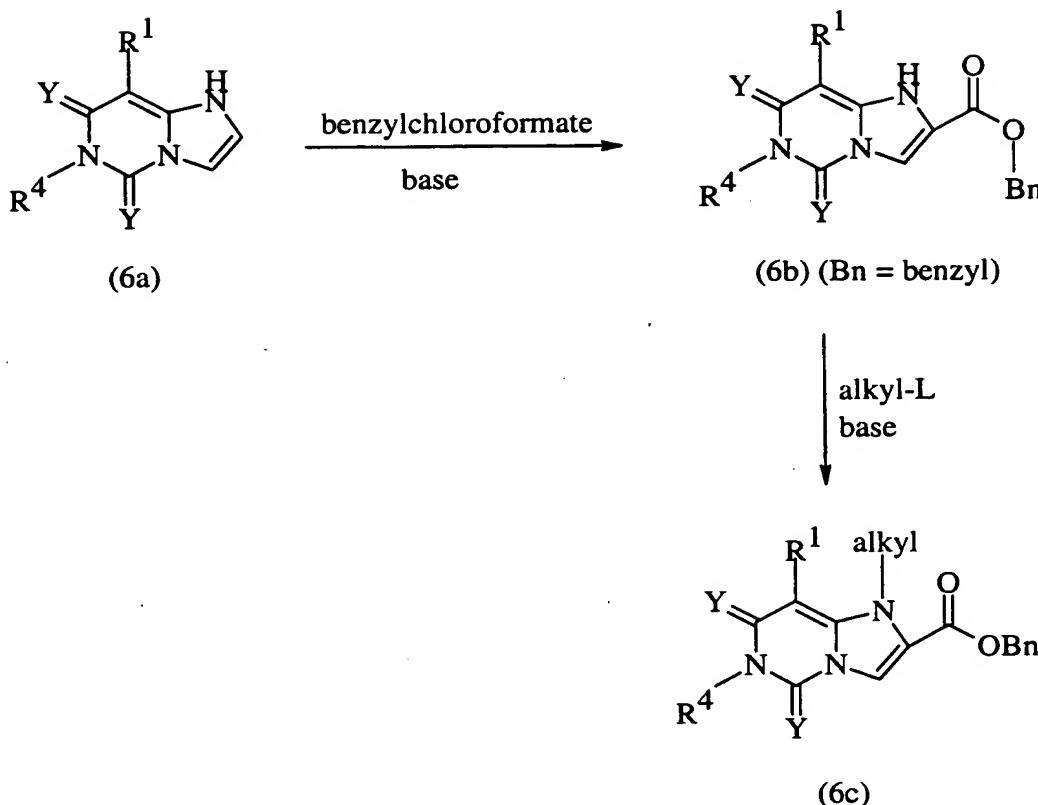
methanol) to give the corresponding oxazolopyrimidine of Formula I ($X = O$, Compound 6a) or the imidazopyrimidine (where $X = NH$ in Compound 6a).

These compounds can then be derivatized at the 2 and 3 positions as described above in Scheme 1, for example as illustrated in Scheme 1b. A cyclized compound (6a) wherein $X = O$ can be reacted with benzylchloroformate in the presence of a base to cause acylation at the 2 position. The 1-amino group can be further derivatized, for instance alkylated or acylated, by standard methods, to give invention compounds such as 6c.

Scheme 1a

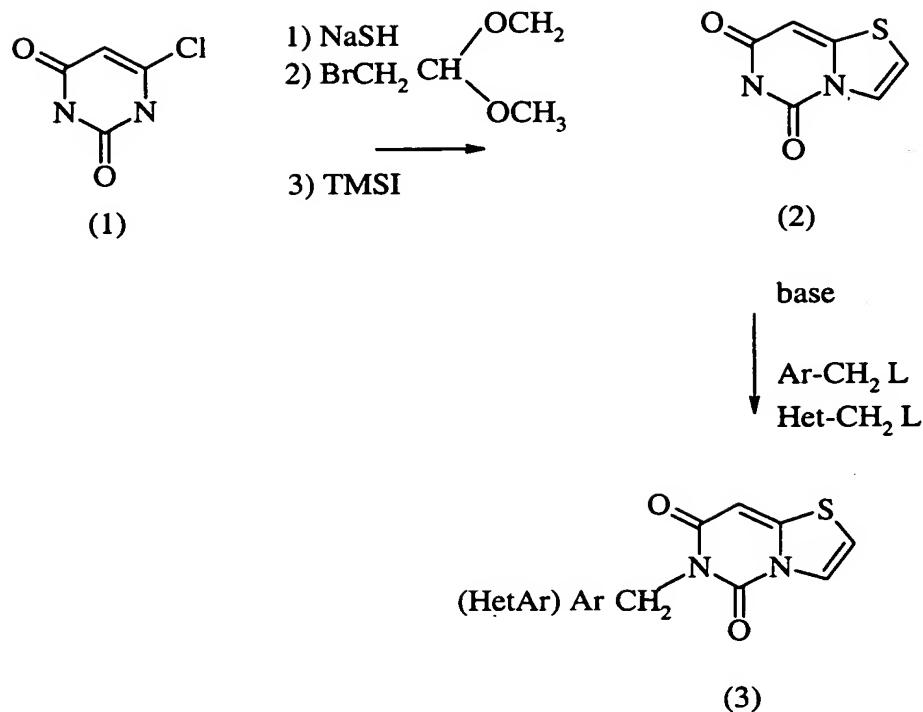


Scheme 1b



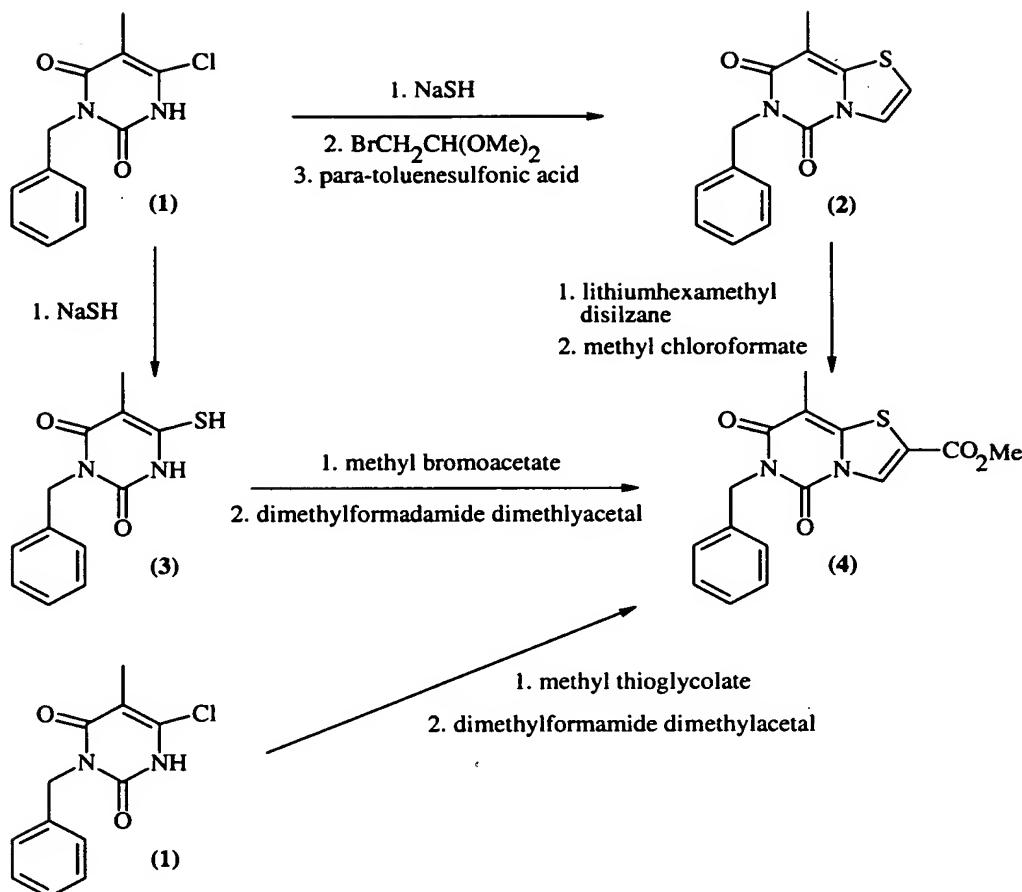
An alternative method for making invention compounds of Formula I is illustrated in Scheme 2. 6-Chloropyrimidine-2,4-dione (1) is reacted with sodium 5 hydrogen sulfide and bromoacetaldehyde dimethyl acetal, and then treated with 1-(trimethylsilyl)iodide (TMSI), to afford a key intermediate, namely 5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine (2). This unsubstituted thiazolopyrimidine readily reacts with alkylating agents such as alkylhalides, arylalkyl halides, and heteroarylalkyl halides, (where L is a good leaving group 10 such as halo) generally in the presence of a base such as triethylamine or cesium carbonate, to effect alkylation at the 6-position to give 6-alkyl, 6-arylalkyl, and 6-heteroarylalkyl (R^4) thiazolopyrimidines of Formula I (3, wherein R^1 , R^2 , and R^3 are hydrogen). These compounds are especially useful as intermediates to 15 2-substituted thiazolopyrimidines (where R^2 in Formula I is other than hydrogen). For example, the compounds (3) are readily converted to invention esters and amides by the general method described above in Scheme 1.

Scheme 2



A method of preparing an intermediate that may be used to prepare a variety of compounds of Formula I is shown below in Scheme 3.

Scheme 3



In Scheme 3, a compound of formula (1) is allowed to react with NaSH to give an intermediate thiol derivative, which is allowed to react with 2-bromoacetaldehyde dimethyl acetal, followed by acid-catalyzed ring closure of the resulting thioether, to give a compound of formula (2). Deprotonation of the compound of formula (2) with lithium hexamethyldisilazane ("LiHMDS"), and quenching of the resulting anion with methylchloroformate gives a compound of formula (4).

Alternately in Scheme 3, the intermediate thiol derivative described above may be allowed to react with methyl bromoacetate, and the resulting thioether allowed to condense and cyclize with dimethylformamide dimethylacetal to give a compound of formula (4).

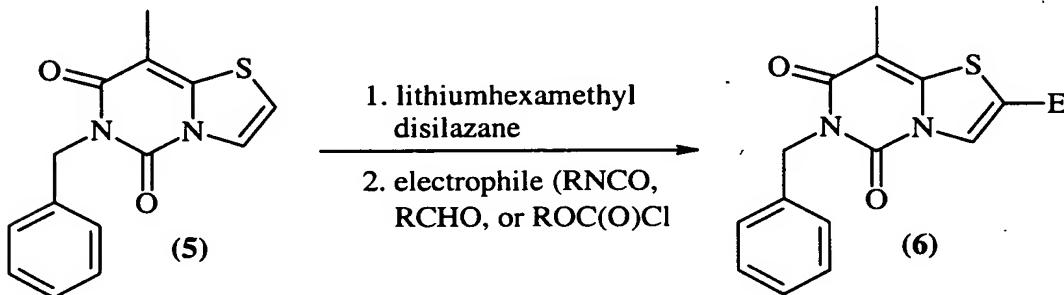
Still alternatively in Scheme 3, the compound of formula (1) may be allowed to react with methyl thioglycolate to give the same intermediate as that

obtained by reaction of the thiol derivative described above with methyl bromoacetate. This intermediate so formed may again be allowed to react with dimethylformamide as described above to give a compound of formula (4).

The compound of formula (4) is a compound of Formula I wherein R² is CO₂CH₃, R⁴ is benzyl, R¹ is methyl, and R³ is H. The compound of formula (4) 5 may be converted by conventional means well known to an artisan of ordinary skill in organic chemistry to compounds of Formula I independently containing esters, amides, or alkynes, to name a few, at R², arylmethyl, substituted arylmethyl, heteroaryl methyl, or substituted heteroaryl methyl, to name a few, at 10 R⁴, and CHO or CH₂OH at R¹. For example, the compound of formula (4) may be converted to a compound of Formula I wherein R² is an amide as shown below in Method 2 of Scheme 4.

Scheme 4

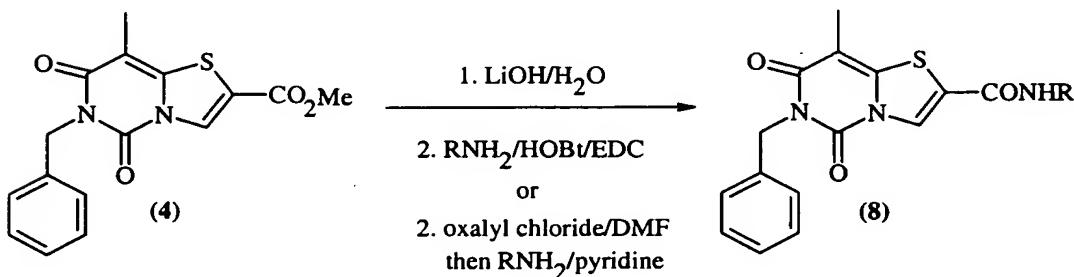
Method 1



E = amide, ester, alcohol

15

Method 2



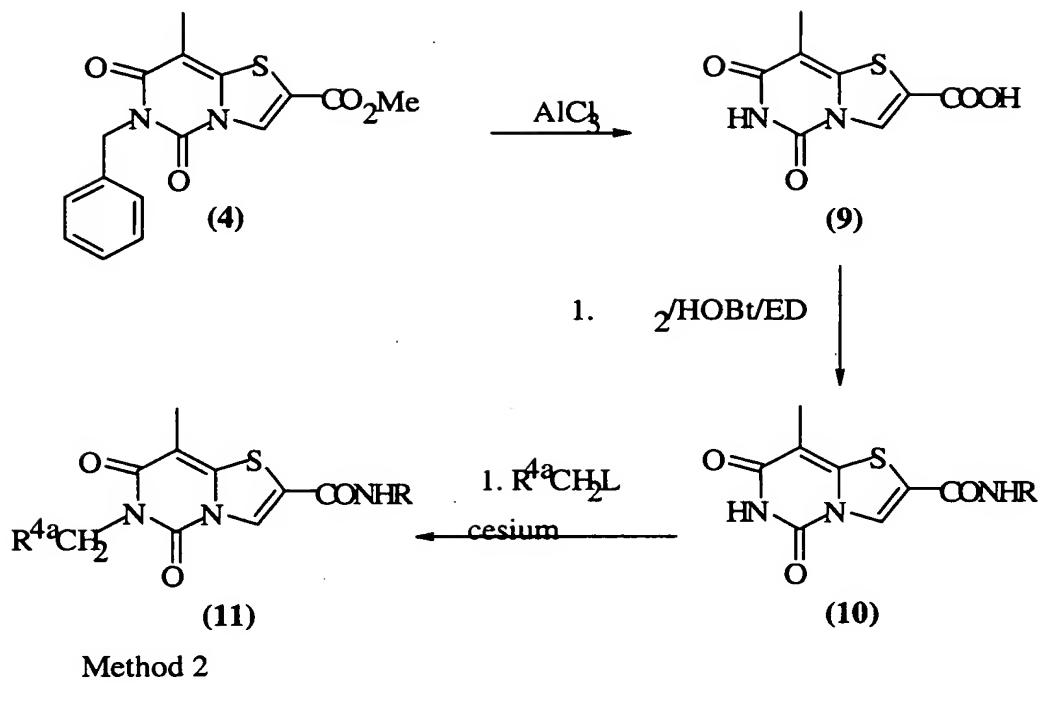
In Method 2 of Scheme 4, the compound of formula (4) is saponified with lithium hydroxide in water, and the resulting carboxylic acid derivative is allowed to couple with an amine of formula RNH_2 , wherein R may be defined as R^5 or R^2 (provided R^2 is not halo), to give an amide of formula (8). The coupling may be
5 accomplished a number of different ways. Two such ways are using a coupling agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (“EDAC”) and 1-hydroxybenzotriazole hydrate (“HOBT”) together with the two reactants, or by first allowing the intermediate carboxylic acid derivative reactant to react with oxalyl chloride in the presence of a catalytic amount of N,N-
10 dimethylformamide (“DMF”), followed by reaction of the resulting acid chloride with RNH_2 in the presence of pyridine.

Alternatively, in Scheme 4, compounds of Formula I wherein R^2 is an amide, ester, or alcohol may be prepared as shown by Method 1. In Method 1 of Scheme 4, a compound of formula (5) may be deprotonated with LiHMDS, and
15 the resulting intermediate anion reacted with an electrophile such as an isocyanate (RNCO), an aldehyde (RCHO), or a chloroformate (ROC(OCl)), wherein R is as defined above, to give an amide, alcohol, or ester, respectively of formula (6).

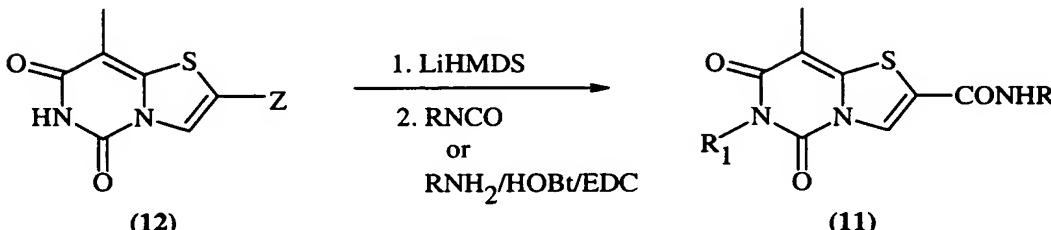
Alternatively the compound of formula (4) prepared according to the procedure illustrated in Scheme 3 may be converted to a compound of Formula I
20 wherein R^2 is an amide and R^4 is arylmethyl, substituted arylmethyl, heteroarylmethyl, substituted heteroarylmethyl, and further, alkenylmethyl, substituted alkenylmethyl, alkynyl methyl, or substituted alkynylmethyl, as illustrated below in Scheme 5.

Scheme 5

Method 1



Method 2



5

Z is H or COOH

In Scheme 5, Method 1, the compound of formula (4) may be debenzylated and demethylated by reacting it with aluminum chloride to give a compound of formula (9). The compound of formula (9) can be allowed to react with an amine of formula RNH_2 , wherein R is as defined above, following the EDAC procedure described above to give a compound of formula (10). The compound of formula (10) may be allowed to react with a compound of formula $\text{R}^{4a}\text{CH}_2\text{L}$, wherein L is a leaving group such as chloro, bromo, iodo, acetoxy, trifluoromethyl sulfonyl, or trifluoroacetyl, and R^{4a}CH_2 is a subset of the set of groups defined above for R^4 wherein the carbon atom in R^4 bonded to the

pyrimidine ring nitrogen atom N-6 is a CH₂ group, in the presence of a base such as cesium carbonate to give a compound of formula (11).

Alternatively in Scheme 5, Method 2, the order of functionalization of the pyrimidine ring substituent groups R² and R⁴ may be reversed from that described above for Method 1 in Scheme 5.

In Scheme 5, Method 2, a compound of formula (12) may be allowed to react with the compound of formula R^{4a}CH₂L, wherein R^{4a} and LX are as defined above, first to give an intermediate containing the group R^{4a}CH₂ for R⁴, followed by conversion to an amide at R² according to the procedure described for Scheme 4, Method 1, when Z is H or conversion to an amide at R² according to the procedure described above for Method 1 of Scheme 5 (for the conversion of a compound of formula (9) to a compound of formula (10)), when Z is COOH.

During the synthesis of some of the invention compounds, it may be desirable to protect reactive functional groups such as hydroxy, amino, and carboxylic groups, so as to avoid unwanted side reactions. The use of protecting groups in synthetic organic chemistry is well-established and is fully described by Greene and Wuts in "Protecting Groups in Organic Synthesis" (John Wiley & Son Press, 3rd ed). Examples of common amino protecting groups include acyl groups such as formyl and acetyl, and arylalkyl groups such as benzyl. Typical hydroxy protecting groups include ether forming groups such as methyl and ethyl, and acyl groups such as acetyl and *tert*-butoxycarbonyl (tBOC). Carboxylic acids generally are protected as esters, for example 2,2,2-trichloroethyl, *tert*-butyl, or benzyl. These protecting groups are readily cleaved by standard methods where desired.

Sulfoxides and sulfones of Formula I, wherein X is SO or SO₂, may be prepared by oxidation of the corresponding sulfides with one or two equivalents of an oxidizing agent such as peracetic acid or meta-chloroperbenzoic acid.

The following detailed examples further illustrate the synthesis of typical invention compounds of Formula I. The examples are representative only and are not to be construed as limiting the invention in any respect. All references cited herein are incorporated by reference.

EXAMPLE 1

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzyl ester

1-Benzyl-pyrimidine-2,4,6-trione

5 Step A: Freshly cut sodium metal (15.9 g, 690 mmol) was dissolved in 100% ethanol, diethylmalonate (53 mL, 349 mmol), and benzylurea (50.33 g, 335 mmol) were added, and the mixture was heated to reflux. The heat was reduced just below reflux, and ethanol (100 mL) was added. The reaction mixture was stirred 3 days at just below ethanol reflux and was then allowed to cool.

10 Water (300 mL) and then 2N HCl (500 mL) were added, and the entire mixture was cooled to 0°C. The resulting solid was collected by filtration, washed with water, and air-dried. Two crops totaling 64.52 g (88%) were obtained.

Calcd for C₁₁H₁₀N₂O₃:

C, 60.55; H, 4.62; N, 12.84.

15 Found: C, 60.65; H, 4.61; N, 12.60.

3-Benzyl-6-chloro-1H-pyrimidine-2,4-dione

Step B: Phosphorus oxychloride (240 mL) was added in small portions over about 0.75 hour to a mixture of 1-benzyl-pyrimidine-2,4,6-trione (47.48 g, 217 mmol) and water (10 mL). Upon completing the addition, the reaction mixture was heated to reflux for 1 hour, then allowed to cool somewhat, then the phosphorus oxychloride was removed on the rotary evaporator, the resulting brown oil was added to ice, and the ice was allowed to slowly melt. The resulting precipitate was collected by filtration, washed with water, slurried in hexanes, collected by filtration, taken up in tetrahydrofuran, dried (magnesium sulfate) filtered, concentrated, and the resulting solid collected by filtration. The product was obtained in 2 portions; total 38.61g (75.2%).

Calcd for C₁₁H₉ClN₂O₂:

C, 55.83; H, 3.83; N, 11.84.

Found: C, 55.76; H, 3.78; N, 11.62.

3-Benzyl-6-(2,2-dimethoxy-ethylsulfanyl)-1H-pyrimidine-2,4-dione

Step C: Ground sodium hydrosulfide hydrate (4.72g, 84 mmol) was added to 3-benzyl-6-chloro-1H-pyrimidine-2,4-dione (4.72g, 20 mmol) in dimethylformamide (20 mL), and the mixture was warmed to 45°C for about 0.25 hour, and then bromacetaldehyde dimethylacetal (11 mL, 93 mmol) was added in portions over about 0.5 hour. The reaction mixture was stirred 3 days at 45°C and was then partitioned between ethyl acetate (400 mL) and sodium bicarbonate solution (200 mL). The layers were separated, and the organic layer washed with water (200 mL) and brine (100 mL) and dried over magnesium sulfate. The solution was filtered and concentrated and triturated with hexanes/ethyl acetate and the solid collected by filtration. The solid was dissolved in methylene chloride, concentrated and triturated (1:1, hexanes/ethyl acetate), filtered and the solid dissolved in methylene chloride, concentrated and triturated (1:1, hexanes/ethyl acetate), filtered again to give 1.128 g of product. An additional 1.76 g was obtained by chromatography of the mother liquors on silica gel using hexanes/ethyl acetate as eluant. Total yield 44.8%.

Calcd for C₁₅H₁₈N₂O₄S:

C, 55.89; H, 5.63; N, 8.69.

Found: C, 55.79; H, 5.32; N, 8.63.

20 6-Benzyl-thiazolo[3,2-c]pyrimidine-5,7-dione

Step D: To a solution of 3-benzyl-6-(2,2-dimethoxy-ethylsulfanyl)-1H-pyrimidine-2,4-dione (1.34 g, 3.83 mmol) in xylene was added 100 mg of para-toluenesulfonic acid. The resulting solution was refluxed for 5 hours while removing methanol using a Dean-Stark trap. The reaction was then cooled to room temperature and purified using flash chromatography to give the desired product as a white solid (1.01 g, 100%). R_f = 0.26 (1:1 hexane/EtOAc); ¹H NMR (CDCl₃) δ 7.20-7.55 (m, 5H), 6.47 (d, 1H, d = 4.6 Hz), 6.00 (s, 1H), 5.18 (s, 2H); MS (ACPI), m/z 259.1 (M⁺+1).

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzyl ester

Step E: To a solution of diisopropylamine in THF (5 mL) at 0°C was added *n*-BuLi (1.6 M, 0.15 mL, 0.24 mmol), and the resulting solution was stirred at 0°C for 10 minutes and cooled to -78°C. A solution of 6-benzyl-thiazolo[3,2-c]pyrimidine-5,7-dione (52 mg, 0.2 mmol) in THF (5 mL) was added, and the resulting solution was stirred at -78° C for 30 minutes. Neat benzylchloroformate (0.041 g, 0.24 mmol) was added dropwise, and the reaction was quenched by addition of NH₄Cl after 30 minutes at -78° C. After extraction with EtOAc, the organic layers were combined and washed with brine, dried, filtered and concentrated *in vacuo*. The residue was purified using flash chromatography to give the desired product as a yellowish solid (became white after trituration with 1:1 hexane/EtOAc, 0.014 g, 18%).

R_f = 0.54 (1:1 hexane/EtOAc); ¹H NMR (CDCl₃) δ 7.84 (s, 1H), 6.92-7.18 (m, 10H), 5.64 (s, 1H), 5.00 (S, 2H), 4.82 (s, 2H); MS (ACPI), *m/z* 392.0 (M⁺⁺1).

EXAMPLE 2

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzyl ester

1-Benzyl-5-methyl-pyrimidine-2,4,6-trione

Step A: Sodium metal (7.68 g, 334 mmol) was dissolved in 100% ethanol (500 mL), benzylurea (25.12 g, 168 mmol) and diethylmethyl malonate (29 mL, 169 mmol) were added, and the mixture was heated at just below ethanol reflux overnight. The reaction mixture was concentrated to remove ethanol, water (200 mL), and 1 N hydrochloric acid (350 mL) were added and an oil separated. The oil would not crystallize and could not be purified by chromatography. The oil was treated with ethanol/sodium ethoxide, (400 mL/7.4 g, 322 mmol) overnight at just below ethanol reflux and was worked up as before to give an oil that would not crystallize. This material was used directly in the next step.

3-Benzyl-6-chloro-5-methyl-1H-pyrimidine-2,4-dione

Step B: The crude pyrimidinedione from above was taken up in tetrahydrofuran (about 10 mL), water (5 mL) was added, concentrated to remove tetrahydrofuran, and phosphorous oxychloride (110 mL) was added in portions over about 45 minutes. Then the mixture was heated at reflux for 2 hours, stirred
5 at room temperature overnight, then the phosphorous oxychloride was removed on the rotary evaporator. Crushed ice (about 300 g) was added, and the mixture was allowed to slowly warm to room temperature and the resulting dark oil solidified on standing. The solid was collected by filtration, washed with water, taken up in tetrahydrofuran, dried over magnesium sulfate, filtered and concentrated to a
10 brown solid. The solid was triturated with hexanes/ethyl acetate, 1:1, v/v, collected by filtration, and washed with hexanes. The product was obtained in 4 portions; total 14 g.(33.2% for the 2 steps).

3-Benzyl-6-(2,2-dimethoxy-ethylsulfanyl)-5-methyl-H-pyrimidine-2,4-dione

Step C: The procedure for Example 1, Step C, was used starting with
15 3-benzyl-6-chloro-5-methyl-1H-pyrimidine-2,4-dione (5.0 g, 20 mmol) from Step B, sodium hydrosulfide hydrate (5.06 g, 90.4 mmol), and bromoacetaldehyde dimethylacetal (13 mL, 110 mmol) to give 3-benzyl-6-(2,2-dimethoxy-ethylsulfanyl)-5-methyl-H-pyrimidine-2,4-dione in two portions; total 2.57 g.
20 (38%).

Calcd for C₁₆H₂₀N₂O₄S:

C, 57.13; H, 5.49; N, 8.33.

Found: C, 57.30; H, 5.50; N, 8.78.

6-Benzyl-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione

Step D: The thioether acetal, 3-benzyl-6-(2,2-dimethoxy-ethylsulfanyl)-
25 5-methyl-H-pyrimidine-2,4-dione, (0.95 g, 2.8 mmol), was treated according to the procedure for Example 1, Step D to give the product, 6-benzyl-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione (0.622 g) as a light tan solid (80.8%).

Calcd for C₁₄H₁₂N₂O₂S:

C, 61.75; H, 4.44; N, 10.29.

30 Found: C, 61.63; H, 4.51; N, 10.19.

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzyl ester

Step E: 6-Benzyl-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione (0.262 g, 0.96 mmol) from Step D was taken up in tetrahydrofuran (25 mL), and lithium hexamethyldisilazane (1.3 mL, 1 M in tetrahydrofuran, 1.3 mmol) was added at -78°C, and the reaction was allowed to proceed for 3 minutes, then benzyl chloroformate (0.5 mL, 3.5 mmol) was added, and the reaction was stirred for 10 minutes at -78°C, ammonium chloride solution (4 mL) was added, and the reaction mixture was allowed to warm until the ice in the flask melted. The reaction mixture was partitioned between ethyl acetate (200 mL) and brine (100 mL). The layers were separated, the organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using hexanes/ethyl acetate, 6:4, v/v as eluant to give the product in 2 portions, 0.158 g (40.5%)

Calcd for C₂₂H₁₈N₂O₄S:

C, 64.92; H, 4.31; N, 6.63.

Found: C, 65.01; H, 4.46; N, 6.89.

EXAMPLE 3

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid pyridin-4-ylmethyl ester hydrochloride

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid methyl ester

Step A: The product from Example 1, Step D (0.518 g, 2.0 mmol), was reacted according to the procedure of Example 2, Step E, using methyl chloroformate (3.0 mL, 39 mmol) in the place of benzyl chloroformate to give the product, 6-benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid methyl ester (0.084 g). An additional 0.26 g of impure product was also obtained (Total yield 54.2%).

Calcd for C₁₅H₁₂N₂O₄S:

C, 56.95; H, 3.82; N, 8.86.

Found: C, 56.87; H, 3.75; N, 8.61.

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid methyl ester may also be obtained according to the following procedure.

Step A-1: The product from Example 1, Step B, namely 3-benzyl-6-chloro-1H-pyrimidine-2,4-dione, (23.7 g, 100 mmol), methyl thioglycolate (11 mL, 130 mmol), and dimethylformamide (100 mL) was heated at 55°C for 1 hour, then triethylamine (15 mL, 108 mmol) was added and the mixture heated at 70°C for 2 hours then stirred 3 days at room temperature. More methyl thioglycolate (4.3 mL, 50 mmol) and triethylamine (4.5 mL, 32 mmol) were added, and the mixture was heated at 70°C for 1 hour. The volatiles were removed on the rotary evaporator at 80°C. The residue was partitioned between ethyl acetate (400 mL) and water (400 mL), and the layers were separated. The organic layer was washed with 10% citric acid solution (100 mL), and brine (100, mL), dried over magnesium sulfate, and filtered and concentrated. The aqueous washes were back-extracted with ethyl acetate (400 mL), the organic layer washed with brine (100 mL), dried, and the organics combined and concentrated to a yellow solid. Trituration with hexanes/ethyl acetate and collection by filtration gave 3-(1-benzyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-ylsulfanyl)-acetic acid methyl ester, 18.6 g, (61%); MS (APCI+), m/z (%): 307(100), 275(40).

Step A-2: To a solution of 3-(1-benzyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-ylsulfanyl)-acetic acid methyl ester (6.12 g, 20 mmol) and tetrahydrofuran (250 mL) at 50°C was added dropwise dimethylformamide dimethylacetal (6 mL, 45 mmol), and the mixture was stirred at 50°C for 0.5 hour and then was heated on the rotary evaporator (no vacuum) at 70°C until all the solvent boiled off. Tetrahydrofuran (200 mL) was added, and the mixture stirred overnight at room temperature. Dioxane (50 mL) was added and then the reaction mixture concentrated to a viscous oil. The oil was filtered through silica gel (70-230 mesh) using hexanes/ethyl acetate, 1:1, v/v to give the product, 6-benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid methyl ester, 2.94 g (46%). MS (APCI+), m/z (%): 317(100), 259(10).

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid

Step B: The product from Example 3, Step A, namely 6-benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid methyl ester, (0.226 g, 0.71 mmol) was taken up in methanol (5 mL), and tetrahydrofuran (5 mL) and 1 M sodium hydroxide solution (0.8 mL, 0.8 mmol) was added at room temperature, and the solution turned orange. Water was added until the volume reached about 25 mL, and no cloudiness occurred. The reaction mixture was allowed to stand about 10 minutes and was then poured into a separatory funnel containing ethyl acetate (200 mL), brine (100 mL), and 1 N HCl solution (3 mL). The layers were separated, dried over magnesium sulfate and concentrated to a yellow solid. The solid was triturated with hexanes/ethyl acetate and the insoluble portion collected by filtration (0.093 g) (44%). This was used directly in the next step.

15 6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid pyridin-4-ylmethyl ester hydrochloride

Step C: The product from Example 3, Step B, namely 6-benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (0.084 g, 0.28 mmol), 4-pyridinemethanol (0.082 g, 0.75 mmol), 4-dimethylaminopyridine (0.014 g, 0.11 mmol), and dichloromethane (5 mL) were stirred at room temperature and dicyclohexylcarbodiimide (0.059 g, 0.29 mmol) was added all at once, and the reaction mixture was cooled to 0°C. The reaction mixture was allowed to slowly warm to room temperature and was stirred overnight. The reaction mixture was concentrated to dryness, chromatographed on silica gel using ethyl acetate as eluant, the product-containing fractions combined and concentrated, and triturated. Dicyclohexylurea was present. The solid was taken up in tetrahydrofuran (about 3 mL), and HCl gas in ether (1 M, 1 mL, 1 mmol) was added and a precipitate formed. The mixture was concentrated to dryness, tetrahydrofuran (about 7 mL) was added and the insoluble portion collected by filtration and washed with tetrahydrofuran and air dried. The product, 6-benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid pyridin-

4-ylmethyl ester hydrochloride was obtained as a light yellow solid (0.0396 g), (33%).

Calcd for C₂₀H₁₅N₃O₄S HCl:

C, 55.88; H, 3.75; N, 9.77.

5 Found: C, 55.49; H, 3.92; N, 9.60.

EXAMPLE 4

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide

To a solution of the product from Example 1, Step D, namely 6-benzylthiazolo[3,2-c]pyrimidine-5,7-dione, (550 mg, 2.13 mmol) in THF (5 mL) was added LiN(TMS)₂ (3.0 mL, 1.0 M, 3.0 mmol), and the resulting solution was stirred at -78°C for 30 minutes. Neat benzylisocyanate (0.34 mL, 2.77 mmol) was added dropwise, and the reaction was stirred at -78°C for 30 minutes and quenched by addition of NH₄Cl solution. After extraction with EtOAc, the organic layers were combined and washed with brine, dried, filtered and concentrated *in vacuo*. The residue was purified using flash chromatography to give the desired product as a yellowish solid (became white after trituration with 1:1 hexane/EtOAc, 0.123 g, 15%). R_f = 0.35 (1:1 hexane/EtOAc); ¹H NMR (d₈-THF) δ 8.16 (s, 1H), 7.99 (S, 1H), 7.06-7.32 (m, 10H), 5.88 (S, 1H), 4.96 (S, 2H), 4.38 (d, 2H, J = 5.6 Hz); MS (ACPI), m/z 392.4 (M⁺+1).

Calcd for C₂₁H₁₇N₃O₃S₁:

C, 64.44; H, 4.38; N, 10.73.

Found: C, 63.95; H, 4.46; N, 10.72.

EXAMPLE 5

6-Benzyl-2-(1-hydroxy-3-phenyl-propyl)-thiazolo[3,2-c]pyrimidine-5,7-dione

To a solution of the product from Example 1, Step D, namely 6-benzylthiazolo[3,2-c]pyrimidine-5,7-dione (720 mg, 2.79 mmol) in THF (5 mL) was added lithiumhexamethyldisilazane (3.91 mL, 1.0 M, 3.91 mmol), and the resulting solution was stirred at -78°C for 30 minutes. Neat hydrocinnamaldehyde

(0.5 mL, 2.77 mmol) was added dropwise, and the reaction was stirred at -78°C for 30 minutes and quenched by addition of NH₄Cl solution. After extraction with EtOAc, the organic layers were combined and washed with brine, dried, filtered and concentrated *in vacuo*. The residue was purified using flash chromatography to give the desired product as a yellowish oil (450 mg, 45%). R_f = 0.60
5 (1:1 hexane/EtOAc); ¹H NMR (d₆-THF) δ 7.47 (d, 1H), 5.92 (S, 1H), 5.14 (S, 2H), 4.64 (t, 1H), 2.70 (m, 2H), 2.01 (m, 2H); MS (ACPI), m/z 393.0 (M⁺⁺1).

EXAMPLE 6

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid biphenyl-4-ylamide

To a solution of the product from Example 1, Step D, namely 6-benzyl-thiazolo[3,2-c]pyrimidine-5,7-dione (380 mg, 1.47 mmol) in THF (5 mL) was added lithiumhexamethyldisilazane (2.2 mL, 1.0 M, 2.2 mmol), and the resulting solution was stirred at -78°C for 30 minutes. Neat 4-biphenylisocyanate (507 mg, 15 2.06 mmol) was added dropwise, and the reaction was stirred at -78°C for 30 minutes and quenched by addition of NH₄Cl solution. After extraction with EtOAc, the organic layers were combined and washed with brine, dried, filtered and concentrated *in vacuo*. The residue was purified using flash chromatography to give the desired product as a white solid, 0.400 g (60%). R_f = 0.80
20 (1:1 hexane/EtOAc); ¹H NMR (DMSO) δ 10.61 (s, 1H), 8.90 (S, 1H), 7.21-7.90 (m, 10H), 6.26 (S, 1H), 5.13 (S, 2H); MS (ACPI+), m/z 454.2 (M⁺⁺1).

EXAMPLE 7

6-Benzyl-2-(hydroxy-phenyl-methyl)-thiazolo[3,2-c]pyrimidine-5,7-dione

To a solution of the product from Example 1, Step D, namely 6-benzyl-thiazolo[3,2-c]pyrimidine-5,7-dione (490 mg, 1.90 mmol) in THF (5 mL) was added lithiumhexamethyldisilazane (2.66 mL, 1.0 M, 2.66 mmol), and the resulting solution was stirred at -78°C for 30 minutes. Benzaldehyde (0.39 mL, 3.80 mmol) was added dropwise, and the reaction was stirred at -78°C for 30 minutes and quenched by addition of NH₄Cl solution. After extraction with

EtOAc, the organic layers were combined and washed with brine, dried, filtered and concentrated *in vacuo*. The residue was purified using flash chromatography to give the desired product as a yellowish oil (200 mg, 29%). $R_f = 0.31$ (1:1 hexane/EtOAc); ^1H NMR ($\text{d}_8\text{-THF}$) δ 7.47 (d, 10H), 5.92 (s, 1H), 5.14 (s, 2H); MS (ACPI), m/z 365.0 ($M^{++}1$).

EXAMPLE 8

6-Benzyl-2-(3-phenyl-propionyl)-thiazolo[3,2-c]pyrimidine-5,7-dione

To a solution of 6-benzyl-2-(1-hydroxy-3-phenyl-propyl)-thiazolo[3,2-c]pyrimidine-5,7-dione (230 mg, 0.59 mmol) in toluene was added activated MnO_2 (10 equivalents). The reaction was refluxed for 30 minutes while removing water using a Dean-Stark trap. The reaction was then cooled to room temperature and purified using flash chromatography to give the desired product as a yellow solid (190 mg, 83%). $R_f = 0.30$ (2:1 hexane/EtOAc); ^1H NMR (CDCl_3) δ 8.24 (s, 1H), 7.20-7.55 (m, 10H), 5.96 (s, 1H), 5.13 (s, 2H), 2.98 (m, 4H); MS (ACPI+), m/z 381.2 ($M^{++}1$).

EXAMPLE 9

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride

The product from Example 3, Step B, namely 6-benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid, (0.280 g, 0.93 mmol), 4-aminomethylpyridine (0.149 g, 1.38 mmol), 1-hydroxybenzotriazole hydrate (0.130 g, 0.96 mmol), dichloromethane (40 mL) and dimethylformamide (about 3 mL) were stirred at 0°C, and dicyclohexylcarbodiimide (0.204 g, 0.99 mmol) was added all at once, and the reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated to dryness with minimal heating, partitioned between ethyl acetate (about 400 mL) and sodium bicarbonate solution. The layers were separated, and the organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was filtered through silica gel

(70-230 mesh) using tetrahydrofuran as eluant. The product-enriched fractions were taken up in tetrahydrofuran and treated with excess hydrogen chloride gas in diethyl ether. The mixture was concentrated to dryness, and diethyl ether was added and the insoluble material collected by filtration. The solid was washed with tetrahydrofuran and dried in vacuo to give the product, 0.055 g.

Calcd for C₂₀H₁₆N₄O₃S₁ HCl H₂O:

C, 54.50; H, 4.33; N, 12.46.

Found: C, 54.66; H, 4.19; N, 12.08.

EXAMPLE 10

10 **6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-fluoro-benzylamide**

The product from Example 2, Step D, namely benzyl-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione, (0.276 g (crude), 1.01 mmol) was taken up in tetrahydrofuran (40 mL) and the solution cooled to -70°C. A solution of 1 M lithiumhexamethyldisilazane in tetrahydrofuran (1.5 mL, 1.5 mmol) was added. The reaction mixture was stirred for 3 minutes at -69°C, and then neat 3-fluorobenzyl isocyanate (0.3 mL, 2.3 mmol) was added all at once. The mixture was stirred 12 minutes at -70°C. The reaction was quenched with ammonium chloride solution and partitioned between ethyl acetate (200 mL) and sodium bicarbonate solution. The layers were separated, the organic layer washed with brine, dried (magnesium sulfate) and concentrated to an orange oil. The oil was chromatographed on silica gel (70-230 mesh) using 7:3, then 2:1, hexanes/ethyl acetate then ethyl acetate as eluant. The product enriched fractions were concentrated and chromatographed again using 7:3, hexanes/ethyl acetate as eluant. The product was obtained upon trituration with diethyl ether/hexanes, 0.0085 g. ¹H-NMR (CDCl₃) δ 7.95 (s, 1H), 7.37 (d, 2H), 7.2-7.4 (m, 5H), 7.26 (d, 1H), 7.01 (bd, 1H), 6.47 (bt, 1H), 5.14 (s, 2H), 4.54 (d, 2H), 1.98 (s, 3H).

EXAMPLE 11

6-Benzoyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide

(2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-yl-sulfanyl)acetaldehyde dimethylacetal

Step A: A suspension of 6-chloro-1H-pyrimidine-2,4-dione (10.0 g, 68.3 mmol) was suspended in dimethylformamide (80 mL) at 40°C. The heat source was removed, and ground sodium hydrogen sulfide (17.3 g, 308 mmol) was added in portions. The temperature was maintained at 40°C for 30 minutes, then bromoacetaldehyde dimethylacetal (36 mL, 308 mmol) was added. The suspension was stirred and heated at 40°C for 18 hours. At the end of the reaction time, the dimethylformamide was removed by vacuum distillation. The residue was triturated with ethyl acetate (100 mL) for 1 hour. The resulting solid was isolated by filtration. The solid was triturated with water (100 mL), filtered, and rinsed with water. The solid was dried in a vacuum at 50°C for 18 hours to give 5.90 g (37%) of (2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-yl-sulfanyl)-acetaldehyde dimethyl acetal. ^1H - NMR (DMSO- d_6) δ 11.22 (s, 1H), 10.92 (s, 1H), 5.43 (s, 1H), 4.53 (t, 1H), 3.31 (d, 3H), 3.27 (d, 3H), 3.18 (d, 2H); MS (APCI-) m/z 231, 199, 143.

Thiazolo[3,2-c]pyrimidine-5,7-dione

Step B: To a suspension of (2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-yl-sulfanyl)acetaldehyde dimethyl acetal (5.90 g, 25.4 mmol) in acetonitrile (400 mL) was added trimethylsilyl iodide (7.2 mL, 50.6 mmol). The mixture was refluxed for 4 hours. The mixture was cooled (ice bath) and isolated by filtration. The solid was rinsed twice with cold acetonitrile, then vacuum dried at 40°C to give 4.08 g (96%) of thiazolo[3,2-c]pyrimidine-5,7-dione.
 ^1H -NMR (DMSO- d_6) δ 11.48 (s, 1H), 7.55 (d, 1H), 6.94 (d, 1H), 5.97 (s, 1H); MS (APCI+) m/z 169.

6-Benzoyl-thiazolo[3,2-c]pyrimidine-5,7-dione

Step C: To a suspension of thiazolo[3,2-c]pyrimidine-5,7-dione (0.506 g, 3.01 mmol) in tetrahydrofuran (20 mL) was added diisopropylethylamine (0.78 mL, 4.5 mmol) followed by benzoyl chloride (0.52 mL, 4.5 mmol). The mixture was stirred at room temperature for 22 hours. The reaction was filtered, and the isolated solid rinsed with ethyl acetate. The combined filtrate was washed with aqueous sodium bicarbonate, dried (Na_2SO_4), and evaporated to an oil. The oil was triturated (hexane:ethyl acetate, 1:1). The resulting solid was purified by flash chromatography (silica gel, dichloromethane:ethyl acetate, 17:3) to give 5 336 mg (41%) of product. TLC R_f = 0.42 ($\text{CH}_2\text{Cl}_2:\text{EtOAc}$, 9:2); ^1H - NMR (DMSO- d_6) δ 8.05 (d, 2H), 7.76 (q, 1H), 7.65 (d, 1H), 7.55-7.64 (m, 2H), 7.08 (t, 1H), 6.24 (s, 1H); MS (APCI+) m/z 273, 189, 169.

10 Calcd for $\text{C}_{13}\text{H}_8\text{N}_2\text{O}_3\text{S}$:
C, 57.35; H, 2.96; N, 10.29.

15 Found: C, 57.39; H, 2.62; N, 10.09.

6-Benzoyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide

Step D: Lithium hexamethyldisilazane (1.7 mL, 1 M in THF, 1.7 mmol) was added to a solution of 6-benzoyl-thiazolo[3,2-c]pyrimidine-5,7-dione 20 (0.319 g, 1.14 mmol) in tetrahydrofuran (25 mL), under nitrogen at -72°C. After 3 minutes, benzyl isocyanate (0.49 mL, 4.0 mmol) was added. The reaction was stirred 15 minutes, then aqueous ammonium chloride was added and the reaction allowed to warm to room temperature. The reaction was partitioned between EtOAc and water. The organic layer was washed with brine, dried (Mg SO_4), and 25 evaporated to a glass. The residue was triturated with hexane:EtOAc, 1:1, and the resulting solid was chromatographed on silica gel eluting with hexanes:THF, 1:1. The isolated product was triturated with diethyl ether to give 81 mg (18%) of 6-benzoyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide: mp 204-207°C (dec.); TLC R_f = 0.34 ($\text{CH}_2\text{Cl}_2:\text{EtOAc}$ 9:2); 30 ^1H -NMR (DMSO- d_6) δ 9.37 (t, 1H), 8.53 (s, 1H), 8.08 (d, 2H), 7.58 (t, 2H),

7.35-7.23 (m, 5H), 6.28 (s, 1H), 4.42 (d, 2H); MS (AP-) *m/z* 404, 323, 300, 271, 257, 231.

Calcd for C₂₀H₁₅N₃O₄S:

C, 62.21; H, 3.73; N, 10.36.

5 Found: C, 62.09; H, 3.82; N, 9.93.

EXAMPLE 12

6-(3,4-Dichlorobenzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide

6-(3,4-Dichlorobenzyl)-thiazolo[3,2-c]pyrimidine-5,7-dione

10 Step A: To a solution of thiazolo[3,2-c]pyrimidine-5,7-dione (1.0 g, 5.95 mmol) in dimethylformamide (20 mL) was added cesium carbonate (2.9 g, 9.1 mmol). The mixture was stirred at room temperature for 15 minutes. To the mixture was added 3,4-dichlorobenzyl chloride (1.2 mL, 8.9 mL) and the reaction stirred at room temperature for 20 hours. The dimethylformamide was removed by vacuum distillation at 60°C. The residue was triturated with EtOAc. The filtrate was evaporated, and the resulting solid was purified by flash chromatography on silica gel eluting with CH₂Cl₂:EtOAc, 19:1 to give 1.252 g (64%) of 6-(3,4-Dichlorobenzyl)-thiazolo[3,2-c]pyrimidine-5,7-dione. TLC R_f = 0.30 (CH₂Cl₂:EtOAc 19:1); ¹H-NMR (DMSO-*d*₆) δ 7.61 (d, 1H), 7.56 (s, 1H), 7.54 (d, 1H), 7.28 (d, 1H), 7.00 (d, 1H), 6.19 (s, 1H), 4.99 (s, 2H); MS (APCI+) *m/z* 331, 329, 327.

6-(3,4-Dichlorobenzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide

25 Step B: Lithium hexamethyldisilazane (0.7 mL, 1 M in THF, 0.7 mmol) was added to a solution of 6-(3,4-dichlorobenzyl)-thiazolo[3,2-c]pyrimidine-5,7-dione (0.233 g, 0.68 mmol) in tetrahydrofuran (10 mL), under nitrogen at -72°C. After 3 minutes benzyl isocyanate (0.25 mL, 2.0 mmol) was added. The reaction was stirred 15 minutes, then aqueous ammonium chloride was added and the reaction allowed to warm to room temperature. To the reaction was added

EtOAc (50 mL). The water layer was removed, and the organic layer was dried (Na₂ SO₄), and evaporated to an oil. The residue was triturated with hexane:EtOAc, 1:1. The resulting filtrate was evaporated to foam. This was chromatographed on silica gel eluting with hexane:EtOAc, 1:1. The isolated product was triturated with diethyl ether and dried in vacuum at 45°C to give 18 mg (5.6%) of 6-(3,4-dichlorobenzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide: mp 216-217° C; TLC R_f = 0.23 (hexane:EtOAc, 1:1); ¹H-NMR (DMSO-*d*₆) δ 9.34 (t, 1H), 8.50 (s, 1H), 7.56 (s, 1H), 7.54 (d, 1H), 7.35-7.25 (m, 6H), 6.22 (s, 1H), 4.99 (s, 2H), 4.41 (d, 2H); MS (APCI+) *m/z* 463, 462, 460, 329, 327, 233.

Calcd for C₂₁H₁₅Cl₂N₃O₃S:

C, 54.79; H, 3.28; N, 9.13.

Found: C, 54.71; H, 3.06; N, 8.93.

EXAMPLE 13

15 **6-(4-Chlorobenzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide**

6-(4-Chlorobenzyl)-thiazolo[3,2-c]pyrimidine-5,7-dione

Step A: To a solution of thiazolo[3,2-c]pyrimidine-5,7-dione (0.505 g, 3.00 mmol) in dimethylformamide (10 mL) was added cesium carbonate (1.47 g, 4.5 mmol). The mixture was stirred at room temperature for 20 minutes. To the mixture was added 4-chlorobenzyl chloride (0.725 g, 4.5 mL) in dimethylformamide (2 mL), and the reaction was stirred at room temperature for 23 hours. The dimethylformamide was removed by vacuum distillation at 60°C. The residue was triturated with EtOAc. The filtrate was evaporated, and the resulting solid was purified by flash chromatography on silica gel eluting with CH₂Cl₂:EtOAc, 9:1 to give 437 mg (50%) of 6-(4-chlorobenzyl)-thiazolo[3,2-c]pyrimidine-5,7-dione: mp 152-153.5; TLC R_f = 0.51 (CH₂Cl₂:EtOAc 17:3); ¹H-NMR (DMSO-*d*₆) δ 7.60 (d, 1H), 7.36-7.7.30 (m, 4H), 7.00 (d, 1H), 6.19 (s, 1H), 4.99 (s, 2H); MS (APCI+) *m/z* 296, 295, 294, 293.

Calcd for C₁₃H₉ClN₂O₂S:

C, 53.34; H, 3.10; N, 9.57.

Found: C, 53.22; H, 3.31; N, 9.31.

6-(4-Chlorobenzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide

Step B: Lithium hexamethyldisilazane (0.96 mL, 1 M in THF, 0.96 mmol) was added to a solution of 6-(3,4-dichlorobenzyl)-thiazolo[3,2-c]pyrimidine-5,7-dione (0.188 g, 0.64 mmol) in tetrahydrofuran (20 mL) under nitrogen at -72°C. After 3 minutes benzyl isocyanate (0.28 mL, 2.2 mmol) was added. The reaction was stirred 20 minutes, then aqueous ammonium chloride was added, and the reaction allowed to warm to room temperature. To the reaction was added EtOAc (50 mL). The water layer was removed, and the organic layer was dried (Na₂SO₄) and evaporated to foam. This was chromatographed on silica gel eluting with hexane:EtOAc, 1:1. The isolated product was triturated twice with diethyl ether and dried in vacuum to give 108 mg (39%) of 6-(4-chlorobenzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide: mp >220° C; TLC R_f = 0.18 (hexane:EtOAc, 1:1); ¹H-NMR (DMSO-*d*₆) δ 9.34 (t, 1H), 8.50 (s, 1H), 7.35-7.23 (m, 9H), 6.22 (s, 1H), 4.99 (s, 2H), 4.40 (d, 2H); MS (APCI+) *m/z* 428, 426, 295, 293, 233.

Calcd for C₂₁H₁₆ClN₃O₃S:

C, 59.22; H, 3.79; N, 9.87.

Found: C, 59.18; H, 3.37; N, 9.34.

EXAMPLE 14

6-(4-Chlorobenzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-dichlorobenzylamide

Lithium hexamethyldisilazane (0.96 mL, 1 M in THF, 0.96 mmol) was added to a solution of 6-(4-chlorobenzyl)-thiazolo[3,2-c]pyrimidine-5,7-dione (0.188 g, 0.64 mmol) in tetrahydrofuran (20 mL), under nitrogen at -72°C. After 3 minutes 3,4-dichlorobenzyl isocyanate (0.33 mL, 2.2 mmol) was added. The

reaction was stirred 15 minutes, then aqueous ammonium chloride was added and the reaction allowed to warm to room temperature. To the reaction was added EtOAc (50 mL). The water layer was removed and the organic layer was dried (Na_2SO_4) and evaporated to an oil. The residue was triturated with
5 hexane:EtOAc, 1:1. The resulting filtrate was evaporated to foam. This was chromatographed on silica gel eluting with hexane:EtOAc, 1:1. The isolated product was triturated with diethyl ether and dried in vacuum at 45°C to give 77 mg (24%) of 6-(4-chlorobenzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-dichloro-benzylamide:
10 mp 218-219° C; TLC R_f = 0.26 (CH_2Cl_2 :EtOAc 17:3); $^1\text{H-NMR}$ (DMSO- d_6) δ 9.37 (t, 1H), 8.48 (s, 1H), 7.60 (d, 1H), 7.55 (s, 1H), 7.36-7.27 (m, 5H), 6.23 (s, 1H), 4.99 (s, 2H), 4.40 (d, 2H); MS (APCI+) m/z 497, 495, 493, 303, 301, 295, 293.
15 Calcd for $\text{C}_{21}\text{H}_{14}\text{Cl}_3\text{N}_3\text{O}_3\text{S}$:
C, 50.98; H, 2.85; N, 8.49.
Found: C, 51.29; H, 2.86; N, 8.35.

EXAMPLE 15

6-(4-Pyridylmethyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide hydrochloride

20 **6-(4-Pyridylmethyl)-thiazolo[3,2-c]pyrimidine-5,7-dione**

Step A: To a solution of thiazolo[3,2-c]pyrimidine-5,7-dione (0.505 g, 3.00 mmol) in dimethylformamide (20 mL) was added sodium hydride (0.39 g, 9.7 mmol, 60% oil dispersion) in small portions over 20 minutes. Over a 1-hour period, 4-bromomethylpyridine hydrobromide (0.92 g, 3.6 mmol) was added. The
25 reaction was stirred at room temperature for 90 minutes. The dimethylformamide was removed by vacuum distillation at 60°C. The residue was triturated with tetrahydrofuran (50 mL) for 16 hours. The mixture was filtered. The filtrate was evaporated, and the resulting solid purified by chromatography on silica gel eluting with CH_2Cl_2 :THF, 2:1. There was recovered 277 mg (33%) of desired
30 product: mp 174-176° C; TLC R_f = 0.24 (CH_2Cl_2 :THF 2:1); $^1\text{H-NMR}$ (DMSO-

d₆) δ 8.45 (d, 2H), 7.61 (d, 1H), 7.24 (d, 2H), 7.01 (d, 1H), 6.21 (s, 1H), 5.03 (s, 2H); MS (AP+) m/z 260.

Calcd for C₁₂H₉N₃O₂S · 0.2 H₂O:

C, 54.83; H, 3.60; N, 15.98.

5 *Found:* C, 55.10; H, 3.60; N, 15.77.

6-(4-Pyridylmethyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide

Step B: Lithium hexamethyldisilazane (0.59 mL, 1 M in THF, 0.59 mmol) was added to a solution of 6-(4-pyridylmethyl)-thiazolo[3,2-c]pyrimidine-5,7-dione (0.100 g, 0.39 mmol) in tetrahydrofuran (15 mL), under nitrogen at -72°C. After 3 minutes benzyl isocyanate (0.12 mL, 0.98 mmol) was added. The reaction was stirred 15 minutes, then aqueous ammonium chloride was added and the reaction allowed to warm to room temperature. To the reaction was added EtOAc (50 mL). The water layer was removed and the organic layer was dried (Na₂SO₄) and evaporated to an oil. This was chromatographed on silica gel eluting with CH₂Cl₂:THF, 2:1 to give 75 mg (49%) of product. This material was combined with other lots and chromatographed in the same manner prior to conversion to the hydrochloride salt. ¹H-NMR (DMSO-*d*₆) δ 9.34 (t, 1H), 8.51 (s, 1H), 8.46 (d, 2H), 7.35-7.23 (m, 7H), 6.25 (s, 1H), 5.03 (s, 2H), 4.41 (d, 2H).

20 **6-(4-Pyridylmethyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide hydrochloride**

Step C: The product from Step B (0.115 g, 0.29 mmol) in tetrahydrofuran (30 mL), under nitrogen, was mixed with anhydrous hydrogen chloride in diethyl ether (0.5 mL, 1 M). The suspension was stirred at room temperature for 16 hours. The resulting solid was isolated by filtration and triturated with water (0.5 mL) for 30 minutes. The solid was isolated and dried in vacuum at room temperature for 22 hours to give 95.2 mg (77%) of the hydrochloride monohydrate: mp > 210°C, ¹H-NMR (DMSO-*d*₆) δ 9.41 (t, 1H), 8.72 (d, 2H), 8.55 (s, 1H), 7.76 (d, 2H), 7.35-7.25 (m, 5H), 5.20 (s, 1H), 4.41 (d, 1H); MS (APCI+) m/z 394, 393, 260.

Calcd for C₂₀H₁₆N₄O₃S · HCl · H₂O.

C, 53.75; H, 4.29; N, 12.54.

Found: C, 54.06; H, 4.24; N, 12.51.

EXAMPLE 16

5 **6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide**

Lithium hexamethyldisilazane (0.67 mL, 1 M in THF, 0.67 mmol) was added to a solution of 6-benzyl-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione (0.122 g, 0.45 mmol) in tetrahydrofuran (10 mL), under nitrogen at -70°C. After 10 minutes benzyl isocyanate (0.20 mL, 0.67 mmol) was added. The reaction was stirred 20 minutes, then aqueous ammonium chloride was added and the reaction allowed to warm to room temperature. Water was added and the mixture stirred overnight. To the reaction was added EtOAc (50 mL). The layers were separated and the organic layer washed with brine, dried (Na₂SO₄), and evaporated to an 15 oil. This material was chromatographed on silica gel eluting with CH₂Cl₂:EtOAc, 9:1. The isolated product was triturated with diethyl ether and dried in vacuum at room temperature for 16 hours to give 62 mg (34%) of 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzylamide. mp 176-178°C; TLC R_f = 0.33 (CH₂Cl₂:EtOAc 9:1); ¹H-NMR (CDCl₃) δ 7.90 (s, 1H), 7.46 (d, 2H), 7.39-7.27 (m, 8H), 6.10 (t, 1H), 5.16 (s, 2H), 4.57 (d, 2H), 1.99 (s, 3H); MS (APCI+) m/z 406, 273.

20 Calcd for C₂₂H₁₉N₃O₃S:

C, 65.17; H, 4.72; N, 10.36.

Found: C, 65.16; H, 4.76; N, 10.15.

25 **EXAMPLE 17**

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxybenzylamide

Lithium hexamethyldisilazane (0.83 mL, 1 M in THF, 0.83 mmol) was added to a solution of 6-benzyl-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione (0.150 g, 0.55 mmol) in tetrahydrofuran (15 mL), under nitrogen at -73°C. After 30 minutes benzyl isocyanate (0.20 mL, 0.67 mmol) was added. The reaction was stirred 20 minutes, then aqueous ammonium chloride was added and the reaction allowed to warm to room temperature. Water was added and the mixture stirred overnight. To the reaction was added EtOAc (50 mL). The layers were separated and the organic layer washed with brine, dried (Na₂SO₄), and evaporated to an oil. This material was chromatographed on silica gel eluting with CH₂Cl₂:EtOAc, 9:1. The isolated product was triturated with diethyl ether and dried in vacuum at room temperature for 16 hours to give 62 mg (34%) of 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxybenzylamide. mp 176-178°C; TLC R_f = 0.33 (CH₂Cl₂:EtOAc 9:1); ¹H-NMR (CDCl₃) δ 7.90 (s, 1H), 7.46 (d, 2H), 7.39-7.27 (m, 8H), 6.10 (t, 1H), 5.16 (s, 2H), 4.57 (d, 2H), 1.99 (s, 3H); MS (APCI+) m/z 406, 273.

3 minutes, 4-methoxybenzyl isocyanate (0.27 mL, 1.9 mmol) was added. The reaction was stirred 20 minutes, then aqueous ammonium chloride was added and the reaction allowed to warm to room temperature. To the reaction was added EtOAc (50 mL). The water layer was removed and the organic layer was, dried (Na₂SO₄) and evaporated to an oil. This material was chromatographed on silica gel eluting with hexane:EtOAc, 2:1. The isolated product was triturated with diethyl ether and dried in vacuum at room temperature for 16 hours to give 108 mg (45%) of 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxybenzylamide: mp 160-162°C; TLC R_f = 0.15 (hexane:EtOAc, 2:1); ¹H-NMR (DMSO-*d*₆) δ 9.23 (t, 1H), 8.52 (s, 1H), 7.29-7.20 (m, 7H), 6.88 (d, 2H), 5.03 (s, 2H), 4.33 (d, 2H), 3.71 (s, 3H), 1.87 (s, 3H); MS (APCI+) *m/z* 436, 273, 121. Calcd for C₂₃H₂₁N₃O₄S: C, 63.43; H, 4.86; N, 9.65.

15 Found: C, 63.35; H, 4.87; N, 9.51.

EXAMPLE 18

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-dichlorobenzylamide

Borane-tetrahydrofuran complex (0.65 mL, 1 M in THF, 0.65 mmol) was added to a solution of 6-benzyl-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione (0.178 g, 0.65 mmol) in tetrahydrofuran (15 mL), under nitrogen at -73°C. To this solution was added lithium hexamethyldisilazane (0.72 mL, 1 M in THF, 0.72 mmol) was added. After 3 minutes 3,4-dichlorobenzyl isocyanate (0.30 mL, 0.204 mmol) was added. The reaction was stirred 40 minutes, then 5% AcOH in EtOH was added and the reaction allowed to warm to room temperature. The solvent was evaporated in vacuum and the residue partitioned between EtOAc (50 mL) and water. The water layer was removed and the organic layer was, dried (Na₂SO₄) and evaporated to a solid. The residue was triturated with diethyl ether overnight. The resulting solid was chromatographed on silica gel eluting with hexane:EtOAc, 1:1. The isolated product was triturated with diethyl ether and dried in vacuum at room temperature for 3.5 hours to give 94 mg (30%) of

6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-dichlorobenzylamide: mp 180-182°C; TLC
R_f = 0.33 (hexane:EtOAc 1:1); ¹H-NMR (DMSO-*d*₆) δ 9.35 (t, 1H), 8.52 (d, 1H),
7.59 (s, 1H), 7.55 (m, 6H), 7.28 (s, 1H), 5.04 (s, 2H), 4.41 (d, 2H), 1.87 (s, 3H);
MS (APCI+) *m/z* 474, 273.

Calcd for C₂₂H₁₇Cl₂N₃O₃S:

C, 55.70; H, 3.61; N, 8.86.

Found: C, 55.61; H, 3.79; N, 8.56.

EXAMPLE 19

6-Benzyl-3-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzyl ester

3-Benzyl-6-(2-oxopropylsulfanyl)-1H-pyrimidine-2,4-dione

Step A: Ground sodium hydrosulfide hydrate (2.36 g, 42 mmol) was added to 3-benzyl-6-chloro-1H-pyrimidine-2,4-dione (2.36g, 10 mmol) in dimethylformamide (12 mL), and the mixture was warmed to 45°C for about 10 minutes and then chloroacetone (4.0 mL, 50 mmol) was added. The reaction mixture was stirred overnight at room temperature and was then partitioned between ethyl acetate (200 mL) and water (200 mL). The layers were separated, and the organic layer washed with water (2 × 100 mL) and dried over magnesium sulfate. The solution was filtered and concentrated to a yellow oil. The oil was chromatographed on silica gel (70-230 mesh) using hexanes/ethyl acetate, 1:1, v/v, as eluant. The product was obtained in several portions as a mixture of the ring-opened and aminal forms. The mixture was used directly in the next step.

6-Benzyl-3-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione

Step B: A mixture of the ring-opened and aminal forms of 3-benzyl-6-(2-oxopropylsulfanyl)-1H-pyrimidine-2,4-dione (0.746 g, 2.6 mmol), xylenes (35 mL), and a catalytic amount of p-toluenesulfonic acid was refluxed with removal of water using a Dean-Stark trap. The reaction mixture was refluxed overnight, concentrated to dryness, and partitioned between ethyl acetate (150 mL) and sodium bicarbonate solution. The layers were separated, the organic

layer dried over magnesium sulfate, filtered and concentrated to a light brown solid. The solid was triturated with hexanes/ethyl acetate to give the product as a tan solid, 0.220 g. An additional 0.258 g was obtained by silica gel filtration of the mother liquors.

5 Calcd for C₁₄H₁₂N₂O₂S:

C, 61.75; H, 4.44; N, 10.29.

Found: C, 61.59; H, 4.43; N, 10.11.

6-Benzyl-3-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzyl ester

10 Step C: The product from Step B, 6-benzyl-3-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione, (0.220 g, 0.81 mmol) was reacted according to the procedure from Example 2, Step E, to give the product, 0.209g (63.7%) in 2 portions.

Calcd for C₂₂H₁₈N₂O₄S:

C, 65.01; H, 4.46; N, 6.89.

Found: C, 65.01; H, 4.47; N, 6.78.

EXAMPLE 20

6-Benzyl-5,7-dioxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-c]pyrimidine-3-carboxylic acid benzyl ester

20 **2,3-Dihydroxypropionic acid benzyl ester**

Step A: To a solution of benzylacrylate (10 g, 61.7 mmol) in acetone (20 mL) and water (7 mL) was added morpholine N-oxide (8.6 g, 73.4 mmol). Osmium tetroxide (3 mL of a 2.5% solution in tertiary butanol) was added and the exothermic reaction moderated by cooling with an ice bath. The reaction was complete in 1 hour. A second portion of benzylacrylate (10 g, 61.7 mmol) and morpholine N-oxide (8.6 g, 73.4 mmol) was added and the reaction mixture stirred at room temperature. When the reaction was complete by TLC, sodium sulfite (10 g, 120 mmol) was added, and the mixture was stirred 0.5 hour. The reaction mixture was extracted with ethyl acetate and washed with 1N hydrochloric acid solution, brine, and dried over magnesium sulfate. The

solution was filtered, concentrated, and distilled (150°C at .1 mm Hg) to give 18.09 g of the product as a colorless oil. This was used directly in the next step.

2,2-Dioxo-2*I*6-[1,2]oxathiolane-4-carboxylic acid benzyl ester

Step B: The product from Step A, namely 2,3-dihydroxypropionic acid benzyl ester (1.00 g, 5.7 mmol), in carbon tetrachloride (20 mL) was treated with thionyl chloride (0.39 mL, 5.36 mmol). Nitrogen gas was bubbled through the solution while refluxing. The reaction was complete in about 0.5 hour.

Acetonitrile (10 mL), ruthenium chloride trihydrate (10 mg), sodium metaperiodate (1.64 g), and water (10 mL) were added and the mixture stirred 0.5 hour. The reaction mixture was diluted with water and ether, and the ether layer dried over magnesium sulfate. The product was obtained as a solid upon filtration through a pad of silica gel; 1.163 g.

Calcd for C₁₀H₁₀O₆S:

C, 47.04; H, 3.96.
15 Found: C, 46.51; H, 3.90.

6-Benzyl-5,7-dioxo-2,3,6,7-tetrahydro-5*H*-thiazolo[3,2-c]pyrimidine-3-carboxylic acid benzyl ester

Step C: 3-Benzyl-6-chloro-1*H*-pyrimidine-2,4-dione (1.083 g, 4.59 mmol) in tetrahydrofuran (10 mL) was treated with potassium t-butoxide (1 M in tetrahydrofuran, 5.6 mL, 5.6 mmol) for 5 minutes. Then 2,2-dioxo-2*I*6-[1,2]oxathiolane-4-carboxylic acid benzyl ester (1.895 g, 7.34 mmol) was added in 1 portion. The reaction mixture was stirred for 2 hours at room temperature and then concentrated in vacuo. Drying under high vacuum afforded a foam. The foam was dissolved in dimethylformamide and sodium hydrosulfide (1.29g, 23 mmol) was added causing an exotherm. The reaction mixture was stirred 2 hours and then treated with 1 N HCl (20 mL) and extracted into ethyl acetate, washed with brine, dried over sodium sulfate, filtered and evaporated. The residue was chromatographed on silica gel using 40% ethyl acetate in hexanes then 70% ethyl acetate in hexanes to give the product; 0.656 g.

30 Calcd for C₂₁H₁₈N₂O₄S:

C, 63.95; H, 4.60; N, 7.10.

Found: C, 63.70; H, 4.70; N, 6.82.

EXAMPLE 21

**6-Benzyl-5,7-dioxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-c]pyrimidine-
5
2-carboxylic acid pyridin-4-ylmethyl ester hydrochloride**

**6-Benzyl-5,7-dioxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-c]pyrimidine-
2-carboxylic acid**

Step A: To a solution of 6-benzyl-5,7-dioxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzyl ester (1.68 g, 4.25 mmol) in a mixture of tetrahydrofuran (48 mL), methanol (14 mL), and water (14 mL) was added at room temperature, lithium hydroxide hydrate (0.37 g, 8.8 mmol). The reaction mixture was stirred 2 hours at room temperature and was partitioned between 1 N hydrochloric acid solution (100 mL) and ethyl acetate (200 mL). The layers were separated, the organic layer washed with sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated to an oil that crystallized from dichloromethane/ethyl ether. The entire mixture was concentrated to dryness and triturated with ethyl ether and the solid collected by filtration; 0.833 g. An additional 0.632 g was obtained from the mother liquors.

Calcd for C₁₄H₁₂N₂O₄S:

20 C, 55.26; H, 3.97; N, 9.21.

Found: C, 55.16; H, 4.09; N, 8.75.

**6-Benzyl-5,7-dioxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-c]pyrimidine-
2-carboxylic acid pyridin-4-ylmethyl ester hydrochloride**

Step B: To a solution of 6-benzyl-5,7-dioxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (.305 g, 1 mmol), 4-hydroxymethylpyridine (0.160 g, 1.47 mmol), 4-dimethylamino pyridine (0.043 g, 0.35 mmol), and tetrahydrofuran (20 mL) at 0°C was added dicyclohexylcarbodiimide (0.224 g, 1.08 mmol), and the mixture was stirred 5 days at room temperature. The reaction mixture was concentrated to dryness, partitioned between ethyl acetate (200 mL) and water (100 mL), the layers

separated, dried over magnesium sulfate, filtered, and concentrated. Some material was insoluble in both layers and was collected by filtration. This solid was treated with HCl gas in diethyl ether (1 M) and the insoluble material collected by filtration; 0.129 g.

5 Calcd for C₂₀H₁₇N₃O₄S · HCl · .5H₂O:

C, 54.48; H, 4.34; N, 9.53.

Found: C, 54.26; H, 4.31; N, 9.35.

EXAMPLE 22

6-Benzyl-5,7-dioxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide

To a solution of 6-benzyl-5,7-dioxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (.304 g, 1 mmol), 4-aminomethylpyridine (0.115 g, 1.06 mmol), 1-hydroxybenzotriazole hydrate (0.140 g, 1.04 mmol), tetrahydrofuran (20 mL) and dimethylformamide (8 mL) at room temperature was added 1-[3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.201 g, 1.05 mmol) and the mixture was stirred 5 days at room temperature. The reaction mixture was concentrated to dryness, partitioned between ethyl acetate (200 mL) and water (100 mL), the layers separated, dried over magnesium sulfate, filtered, and concentrated to a yellow oil. The oil was triturated with hexanes/ethyl acetate and the resulting solid collected by filtration; 0.198 g.

Calcd for C₂₀H₁₈N₄O₃S · .5H₂O:

C, 59.54; H, 4.75; N, 13.89.

Found: C, 59.85; H, 4.71; N, 13.97.

25

EXAMPLE 23

6-Benzyl-1,5,7-trioxo-1,2,3,5,6,7-hexahydro-1*H*⁴-thiazolo[3,2-c]pyrimidine-3-carboxylic acid benzyl ester

A mixture of 6-benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid benzyl ester (2.55 g, 6.46 mmol), 4Å molecular sieves (3 g) in dichloromethane 150 mL was stirred at 0°C. m-Chloroperbenzoic

acid (2.53 g, 15.2 mmol) was added in 3 portions at 0, 2, and 14 hours. After 20 hours the reaction was filtered, concentrated, and taken up in ethyl acetate. The organic layer was washed with sodium bicarbonate solution (2×200 mL), brine, and dried over magnesium sulfate. The mixture was filtered, concentrated, and chromatographed on silica gel eluting with 5% acetone in dichloromethane to afford the title compound (1.69 g, 64%).

Calcd for $C_{21}H_{18}N_2O_5S$:

C, 61.45; H, 4.42; N, 6.83.

Found: C, 61.31; H, 4.44; N, 6.69.

10

EXAMPLE 24

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carbothioic acid benzylamide

15

Lithium hexamethyldisilazane (0.8 mL, 1 M in THF, 0.8 mmol) was added to a solution of 6-benzyl-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione (0.136 g, 0.50 mmol) in tetrahydrofuran (20 mL), under nitrogen at -68°C . After 3 minutes benzyl isothiocyanate (0.20 mL, 1.5 mmol) was added. The reaction was stirred 14 minutes, then aqueous ammonium chloride was added and the reaction allowed to warm to room temperature. To the reaction was added EtOAc (200 mL). The layers were separated and the organic layer washed with brine, dried over magnesium sulfate, and evaporated to an orange oil. This material was chromatographed 2 times on silica gel eluting with hexanes:EtOAc, 7:3, to give the product as a yellow solid; 0.045 g.

20

Calcd for $C_{22}H_{19}N_3O_2S_2$:

C, 62.69; H, 4.54; N, 9.97.

25

Found: C, 62.38; H, 4.48; N, 9.51.

EXAMPLE 25

6-Benzyl-3-ethoxy-2,3-dihydro-oxazolo[3,2-c]pyrimidine-5,7-dione 3-Benzyl-6-(2,2-diethoxy-ethoxy)-1H-pyrimidine-2,4-dione

30

Step A: A solution of the sodium alkoxide of 2-hydroxyacetaldehyde diethyl acetal was prepared from sodium hydride (1.74 g (60% in mineral oil,

43.5 mmol)) and 2-hydroxyacetaldehyde diethyl acetal (5.4 g, 40.3 mmol) in dimethylformamide (40 mL) at room temperature. The alkoxide solution was warmed to 50°C and then 3-benzyl-6-chloro-1H-pyrimidine-2,4-dione (4.70 g, 20 mmol) was added, and the mixture was heated to 80°C overnight and then was 5 heated to 110°C overnight. A second portion of alkoxide (from 2.70 g alcohol and 0.97 g sodium hydride (60% in mineral oil)) in dimethylformamide (10 mL) was added, and the reaction mixture was stirred overnight at 110°C. The reaction 10 mixture was cooled, concentrated, and partitioned between ethyl acetate (400 mL) and sodium bicarbonate solution (400 mL). The layers were separated, the organic layer washed with water (2 × 100 mL), brine (100 mL), and dried over magnesium sulfate, filtered, and concentrated to an oil. The oil was filtered through silica gel (70-230 mesh) using tetrahydrofuran as eluant and was then filtered through silica 15 gel (70-230 mesh) again using ethyl acetate as eluant. Several portions of product were obtained. $^1\text{H-NMR}$ (CDCl_3) δ 8.93 (bs, 1H), 7.22-7.44 (m, 5H), 5.10 (s, 1H), 5.05 (s, 2H), 4.76 (t, 1H), 3.98 (d, 2H), 3.69-3.78 (m, 2H), 3.55-3.63 (m, 2H), 1.22 (m, 6H).

This material was used directly in the next step.

6-Benzyl-3-ethoxy-2,3-dihydro-oxazolo[3,2-c]pyrimidine-5,7-dione

Step B: A mixture of 3-benzyl-6-(2,2-diethoxy-ethoxy)-1H-pyrimidine-20 2,4-dione (3.14 g, 9.4 mmol), xylenes (70 mL), and a catalytic amount of p-toluenesulfonic acid hydrate was heated to reflux employing a Dean-Stark trap. After 4 hours, no starting material remained. The reaction mixture was 25 concentrated to dryness and the oil/gum taken up in ethyl acetate (200 mL) and was washed with sodium bicarbonate solution, dried over magnesium sulfate, filtered and concentrated to a brown oil/gum. Upon addition of ethyl acetate a small amount of precipitated formed and was collected; 0.036 g. $^1\text{H-NMR}$ ($\text{DMSO}-d_6$) δ 8.93 (bs, 1H), 7.1-7.3 (m, 5H), 5.96 (d, 1H), 4.83 (dd, 2H), 4.6-4.8 (m, 2H), 3.67-3.85 (m, 2H), 1.09 (t, 3H).

EXAMPLE 26

6-Benzyl-3-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid methyl ester

Step A: Ground sodium hydrosulfide hydrate (4.35g, 78 mmol) was added
5 to 3-benzyl-6-chloro-1H-pyrimidine-2,4-dione (4.72 g, 20 mmol) in
dimethylformamide (15 mL), and the mixture was warmed to 44°C and then neat
methyl-2-chloroacetoacetate (10 mL, 82 mmol) was added in portions over about
10 minutes. The reaction mixture was stirred 0.5 hour at 50°C and was then
partitioned between ethyl acetate (450 mL) and sodium bicarbonate solution
10 (100 mL) and water (200 mL). The layers were separated and the organic layer
washed with water (2 × 200 mL) and brine (100 mL) and dried over magnesium
sulfate. The solution was filtered and concentrated and triturated with
hexanes/ethyl acetate, 1:1, v/v, and the solid collected by filtration, 2.17 g.
A second crop was obtained from the mother liquors, 0.68 g, (41%). MS (APCI+)
15 *m/z* (%): 349.1(100), 317.1(50).

Step B: The product from Example 26, Step A, (0.837 g, 2.4 mmol) was
heated to reflux in toluene (50 mL) in the presence of a catalytic amount of para-
toluenesulfonic acid hydrate employing a Dean-Stark trap for the azeotropic
removal of methanol. The reaction mixture was refluxed 9 hours then
concentrated to an oil. The oil was filtered through silica gel (70-230 mesh) using
20 hexanes/ethyl acetate, 12:1, v/v as eluant. The product, 6-benzyl-3-methyl-
5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid methyl
ester, was obtained as a white solid, 0.142 g (18 %). MS (APCI+), *m/z* (%):
331.1(100).

25

EXAMPLE 27

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 2,4-dichloro-benzylamide

Employing the procedure of Example 2, Step E, 6-benzyl-8-methyl-
thiazolo[3,2-c]pyrimidine-5,7-dione (0.272g, 1.0 mmol) was taken up in
30 tetrahydrofuran (10 mL) and lithium hexamethyldisilazane (1.5 mL, 1 M in
tetrahydrofuran, 1.5 mmol) was added at -78°C, and the reaction was allowed to

proceed for 3 minutes; then 2,4-dichlorobenzyl isocyanate (0.5 mL, 3.4 mmol) was added, and the reaction was stirred for 15 minutes at -78°C, ammonium chloride solution was added, and the reaction mixture was partitioned between ethyl acetate and brine. The layers were separated, the organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using hexanes/ethyl acetate, 65:35, v/v as eluant to give the product, 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 2,4-dichloro-benzylamide, as a white solid upon trituration with hexanes/ethyl acetate, 100 mg (21%). MS (APCI+), m/z (%): 476.1(60), 474.1 (80) 273.1 (100).

EXAMPLE 28

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-methyl-benzylamide

Employing the procedure of Example 2, Step E, 6-benzyl-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione (0.272g, 1.0 mmol) was taken up in tetrahydrofuran (10 mL), and lithium hexamethyldisilazane (1.5 mL, 1 M in tetrahydrofuran, 1.5 mmol) was added at -78°C, and the reaction was allowed to proceed for 3 minutes; then 3-methylbenzyl isocyanate (0.35 mL, 2.7mmol) was added, and the reaction was stirred for 15 minutes at -78°C, ammonium chloride solution was added, and the reaction mixture was partitioned between ethyl acetate and brine. The layers were separated, the organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using hexanes/ethyl acetate, 65:35, v/v as eluant to give the product, 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-methyl-benzylamide, as a white solid upon trituration with hexanes/ethyl acetate, 120 mg (29%). MS (APCI+), m/z (%): 420.1(100), 273.1 (75).

EXAMPLE 29

6-Benzyl-2-(1-hydroxy-3-phenyl-allyl)-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione

Employing the procedure of Example 2, Step E, 6-benzyl-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione (0.407 g, 1.5 mmol) was taken up in tetrahydrofuran (12 mL) and lithium hexamethyldisilazane (3.2 mL, 1 M in tetrahydrofuran, 3.2 mmol) was added at -72°C, and the reaction was allowed to proceed for 3 minutes, then trans-cinnamaldehyde (0.5 mL, 4.0 mmol) was added, and the reaction was stirred for 15 minutes at -72°C, ammonium chloride solution (3 mL) was added, and the reaction mixture was allowed to slowly warm to room temperature and was then partitioned between ethyl acetate (150 mL) and brine (50 mL). The layers were separated, the organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using hexanes/ethyl acetate, 70:30, v/v as eluant to give the product, 6-benzyl-2-(1-hydroxy-3-phenyl-allyl)-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione, 24.8 mg (4.1%). MS (APCI+), m/z (%): 405.1(100).

EXAMPLE 30

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

Procedure 1:

Employing the procedure of Example 2, Step E, 6-benzyl-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione (0.407 g, 1.5 mmol) was taken up in tetrahydrofuran (40 mL) and lithium hexamethyldisilazane (1.8 mL, 1 M in tetrahydrofuran, 1.8 mmol) was added at -72°C, and the reaction was allowed to proceed for 3 minutes; then 4-fluorobenzyl isocyanate (0.336 g, 2.2 mmol) in tetrahydrofuran (0.5 mL) was added, and the reaction was stirred for 14 minutes at -72°C, ammonium chloride solution (2 mL) was added, and the reaction mixture was allowed to slowly warm until the ice in the reaction flask melted. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with brine (50 mL). The layers were separated, the organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using

hexanes/ethyl acetate, 70:30, v/v as eluant, then chromatographed a second time using hexanes/ethyl acetate, 1:1, v/v as eluant to give the product, 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide, 50 mg in 2 portions (7.9%). MS (APCI+), m/z (%):
5 424.1(100), 273.1 (50).

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide (prepared by carbodiimide coupling)

Procedure 2:

The product of Example 33, Step B (see below), namely 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (158 mg, 0.50 mmol) (see below) was dissolved in dimethylformamide (4.5 mL). Added were 4-fluorobenzyl amine (84 mg, 67 mmol), 1-hydroxybenzotriazole hydrate (69 mg, 0.50 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (104 mg, 0.54 mmol). The reaction mixture
10 was stirred overnight at room temperature. The reaction mixture was partitioned between ethyl acetate (200 mL) and water (100 mL), and the layers were separated. The organic layer was washed with saturated sodium bicarbonate solution (50 mL) and brine (50 mL). The layers were separated and the organic layer dried over magnesium sulfate, filtered, and evaporated in vacuo. The
15 resulting was triturated with ethyl ether and collected by filtration, 0.182g (86%).
20

EXAMPLE 31

6-Benzyl-2-(1-hydroxy-3-phenyl-prop-2-ynyl)-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione

Employing the procedure of Example 2, Step E, 6-benzyl-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione (1.08 g, 4.0 mmol) was taken up in tetrahydrofuran (30 mL) and lithium hexamethyldisilazane (6.0 mL, 1 M in tetrahydrofuran, 6.0 mmol) was added over 2 minutes at -70°C, and the reaction was allowed to proceed for 2 minutes, then phenylpropargyl aldehyde (0.822 g, 6.3 mmol) was added, and the reaction was stirred for 13 minutes at -70°C,
25 ammonium chloride solution was added, and the reaction mixture was allowed to slowly warm until the ice in the reaction flask melted and was then partitioned
30

between ethyl acetate (200 mL) and brine (50 mL). The layers were separated, the organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was filtered through silica gel using methylene chloride, then hexanes/ethyl acetate, 70:30, v/v as eluant to give the product, 6-benzyl-
5 2-(1-hydroxy-3-phenyl-prop-2-ynyl)-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione, 419 mg, in 2 portions (26%); MS (APCI+), m/z (%): 403.2(100), 387.2 (25).

EXAMPLE 32

10 **6-Benzyl-8-formyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide**

Step A: Employing the procedure of Example 2, Step E, the product of Example 1, Step D, namely 6-benzyl-thiazolo[3,2-c]pyrimidine-5,7-dione (3.56 g, 13.8 mmol) was taken up in tetrahydrofuran (150 mL), and lithium hexamethyldisilazane (21 mL, 1 M in tetrahydrofuran, 6.0 mmol) was added over
15 7 minutes at -73°C to -70°C, and the reaction was allowed to proceed for 1 minute; then 4-methoxybenzyl isocyanate (5.06 g, 31 mmol) in tetrahydrofuran (2 mL) was added as rapidly as possible, keeping the temperature below -60°C, and the reaction was stirred for 16 minutes at -70°C; ammonium chloride solution was added, and the reaction mixture was then partitioned between ethyl acetate
20 (200 mL) and brine (50 mL). The layers were separated, the organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was filtered through silica gel using hexanes/ethyl acetate, 70:30, v/v as eluant to give the product as a mixture, 1.044 g, in 2 portions (18%). The product could not be purified by trituration with ethyl ether, and was used directly in the next step. MS
25 (APCI+), m/z (%): 422.1(100), 259.1 (65).

Step B: The product from Step A, (0.523 g, 1.24 mmol) was taken up in dimethylformamide (7.5 mL) and phosphorus oxychloride (1 mL) was added and the mixture stirred overnight at room temperature. The reaction mixture was then heated on the rotary evaporator (no vacuum) at 90°C for 3 hours and was then
30 concentrated. The resulting dark oil was partitioned between ethyl acetate (200 mL) and aqueous sodium bicarbonate/sodium chloride (100 mL), the layers

separated, the organic layer dried over magnesium sulfate, filtered, and concentrated. The residue was filtered through silica gel (70-230 mesh) using hexanes/ethyl acetate, 1:1, v/v to give the product, 6-benzyl-8-formyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxybenzylamide, 0.083 g (14.9%). MS (APCI+), m/z (%): 450.1(100), 287.1 (80).

EXAMPLES 33 and 33a

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (Example 33)

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid methyl ester (Example 33a)

Step A: Employing the procedure of Example 3, Step E, 6-Benzyl-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione (554 mg, 2.03 mmol) in tetrahydrofuran (40 mL) under N₂ at -73°C was treated with lithium hexamethyldisilazane (3.05 mL 1 M in THF, 3.05 mmol). After 3 minutes, methyl chloroformate was added. After 20 minutes, saturated NH₄Cl was added and the reaction allowed to warm to room temperature. The water layer was removed, the organic layer was dried (Na₂SO₄), decanted and evaporated in vacuo to an oil. Chromatography on silica gel eluting with Hexane:EtOAc, 3:1 gave 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid methyl ester (Example 33a) (53%); MS (APCI+), m/z (%): 331(100), 273(20).

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid methyl ester also may be prepared according to the procedure of Step A-1 below.

Step A-1: The product from Example 2, Step B, namely 3-benzyl-6-chloro-5-methyl-1H-pyrimidine-2,4-dione, (5.02, 20 mmol) was reacted according to the procedure for Example 3, Step A-1, using cesium carbonate in place of triethylamine to give (1-benzyl-5-methyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-ylsulfanyl)-acetic acid methyl ester, 3.165 g (49 %). MS (APCI+), m/z (%): 321(100), 289(90).

Step A-2: 1-Benzyl-5-methyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-ylsulfanyl)-acetic acid methyl ester from Step A-1 above, 0.320 g, 1 mmol) was

reacted according to the procedure of Example 3, Step A-2 to give benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid methyl ester (Example 33a), 0.203 g (61%). MS (APCI+), m/z (%): 331(100).

5 **6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid**

Step B: The product from Step A (350 mg, 1.06 mmol) was dissolved in tetrahydrofuran (20 mL). To the solution was added methanol (10 mL) and water (10 mL). To the solution was added lithium hydroxide hydrate (134 mg, 3.2 mmol) in water (10 mL). After 10 minutes at room temperature, the reaction 10 was poured into a separatory funnel of EtOAc and water. Hydrochloric acid (10 mL of 1 M, 10 mmol) was added. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried (Na_2SO_4), and evaporated in vacuo to an oil. The material was 15 triturated with diethyl ether to give 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (Example 33) (86%); MS (APCI+), m/z (%): 317(50), 273(100).

EXAMPLE 34

20 **6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (1H-indol-5-ylmethyl)-amide**

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (80 mg, 0.25 mmol) was dissolved in tetrahydrofuran (10 mL). Added in order were 5-aminomethylindole (43 mg, 0.29 mmol), 1-hydroxybenzotriazole hydrate (55 mg, 0.41 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (57 mg, 0.30 mmol). The mixture was stirred for 2.5 hours at room temperature. The tetrahydrofuran was evaporated in vacuo and the residue partitioned between EtOAc and water. The organic layer was washed twice with 1 M HCl, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed on silica gel eluting with $\text{CH}_2\text{Cl}_2:\text{EtOAc}$, 9:1. The resulting solid was triturated with 25 diethyl ether and dried in a vacuum to give 6-benzyl-8-methyl-5,7-dioxo-30

6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (1H-indol-5-ylmethyl)-amide (46%); mp 189-191; MS (APCI+), m/z (%): 445(20), 273(20), 130(100).

EXAMPLE 35

5 **6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (thiazol-4-ylmethyl)-amide hydrochloride**

10 **C-Thiazol-4-yl-methylamine**
Step A: C-Thiazol-4-yl-methylamine was made from 4-chloromethyl-thiazole in 2 steps using the procedure of Culbertson, T.P., Domagala, J.M., Peterson, P., Bongers, S., Nichols, J.B.; *J. Heterocyclic Chemistry* 1987;24:1509.

15 **6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (thiazol-4-ylmethyl)-amide hydrochloride**
Step B: 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (333 mg, 1.05 mmol) was dissolved in dimethylformamide (10 mL). Added in order were 4-aminomethylthiazole (138 mg, 1.21 mmol), 1-hydroxybenzotriazole hydrate (148 mg, 1.10 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (210 mg, 1.10 mmol). The mixture was stirred for 16 hours at room temperature. The dimethylformamide was evaporated in vacuo and the residue partitioned between EtOAc and water. The organic layer was washed twice with water, twice with 10% sodium carbonate, then brine. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was crystallized from ethyl acetate to give 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (thiazol-4-ylmethyl)-amide (60% yield). The material was dissolved in tetrahydrofuran (10 mL) and treated with 1 M HCl in diethyl ether (1 mL, 1 mmol). Filtration gave 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (thiazol-4-ylmethyl)-amide hydrochloride (91%). MS (APCI+), m/z (%): 413(100), 273(10).

EXAMPLE 36

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride

The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-
5
6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid, (0.32 mmol, based
on amount of starting ester from the previous step) was dissolved in
tetrahydrofuran (15 mL), and 1-hydroxybenzotriazole hydrate (47 mg,
0.35 mmol), 4-aminomethylpyridine (54 mg, 0.5 mmol) were added. The reaction
mixture was cooled to zero degrees, and dicyclohexylcarbodiimide (77 mg,
10
0.37 mmol) was added. The reaction mixture was allowed to slowly warm to room
temperature and was then stirred overnight at room temperature. The reaction
mixture was diluted to 100 mL with ethyl acetate and was washed with saturated
sodium bicarbonate solution, dried over magnesium sulfate, filtered and
concentrated. The residue was chromatographed on silica gel (70-230 mesh) using
15
ethyl acetate as eluant. The product-containing fractions were concentrated and
treated with HCl gas in ether to give the product as a white solid in 2 portions,
0.074 g (52%). MS (APCI+), m/z (%): 407.1(100), 273.1 (30).

EXAMPLES 37 and 37a

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide (Example 37); and
20
6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide hydrochloride (Example 37a)

The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-
25
6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (158 mg, 0.5 mmol)
was dissolved in dimethylformamide (4.5 mL). Added were 2-methoxy-
4-aminomethylpyridine (73 mg, 0.54 mmol), 1-hydroxybenzotriazole hydrate
(68 mg, 0.5 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide
hydrochloride (102 mg, 0.53 mmol). The mixture was stirred for 3 days at room
30
temperature. The reaction mixture was partitioned between ethyl acetate (200 mL)
and water (100 mL). The organic layer was washed with water (100 mL),
saturated sodium bicarbonate solution (50 mL), and brine (50 mL). The layers

were separated, and the organic layer was dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was chromatographed on silica gel (70-230 mesh) using ethyl acetate as eluant. The product-containing fractions were concentrated and the residue triturated with ethyl ether/ethyl acetate to give

5 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide, 41.7 mg, (19%) (Example 37). Treatment of the mother liquors with HCl gas in ethyl ether gave

10 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methoxy-pyridin-3-ylmethyl)-amide hydrochloride (Example 37a), 45 mg (19%). MS (APCI+), m/z (%): 437.2(100), 273.1 (70).

EXAMPLE 38

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (imidazo[2,1-b]thiazol-6-ylmethyl)-amide

The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (158 mg, 0.5 mmol) was dissolved in dimethylformamide (4 mL). Added were C-imidazo[2,1,b]thiazol-6-yl-methylamine(122 mg, 65 mmol), 1-hydroxybenzotriazole hydrate (72 mg, 0.53 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (96 mg, 0.50 mmol). The mixture was stirred for 3 days at room temperature. The reaction mixture was concentrated at 60°C on the rotary evaporator. The residue was partitioned between ethyl acetate/tetrahydrofuran, 1:1, v/v, (200 mL) and water (250 mL). The layers were separated, and the organic layer was washed with saturated sodium bicarbonate solution, the layers were separated and the organic layer dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was chromatographed on silica gel (70-230 mesh) using ethyl acetate as eluant. The product-containing fractions were concentrated and the residue triturated with ethyl ether/ethyl acetate/tetrahydrofuran to give 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (imidazo[2,1-b]thiazol-6-ylmethyl)-amide, 143 mg (63%). MS (APCI+) m/z (%): 452.1(100), 273.1 (70).

EXAMPLE 39

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (1-methyl-1H-pyrazol-4-ylmethyl)-amide

The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-
5
6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (158 mg, 0.5 mmol)
was dissolved in dimethylformamide (4.5 mL). Added were C-(1-methyl-1H-
pyrazol-4-yl)methylamine (56 mg, 51 mmol), 1-hydroxybenzotriazole hydrate
(71 mg, 0.53 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide
hydrochloride (96 mg, 0.50 mmol). The mixture was stirred for 3 days at room
10
temperature. The reaction mixture was concentrated at 58°C on the rotary
evaporator. The residue was partitioned between ethyl acetate (200 mL) and water
(200 mL). The layers were separated, and the organic layer was washed with
saturated sodium bicarbonate solution (100 mL), the layers were separated and the
organic layer dried over magnesium sulfate, filtered, and evaporated in vacuo. The
15
residue was chromatographed on silica gel (70-230 mesh) using ethyl acetate as
eluant. The product-containing fractions were concentrated and the residue
triturated with ethyl ether to give 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-
thiazolo[3,2-c]pyrimidine-2-carboxylic acid (1-methyl-1H-pyrazol-4-ylmethyl)-
amide, 133 mg (65%). MS (APCI+), m/z (%): 410.2(100), 273.1 (80).

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EXAMPLE 40

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid prop-2-ynylamide

The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-
6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (157 mg, 0.5 mmol)
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was dissolved in dimethylformamide (5 mL). Added were propargyl amine
(46 mg, 83 mmol), 1-hydroxybenzotriazole hydrate (71 mg, 0.53 mmol) and
1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (98 mg,
0.51 mmol). The mixture was stirred for 3 days at room temperature. The reaction
mixture was concentrated on the rotary evaporator. The reaction mixture was
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partitioned between ethyl acetate (200 mL) and saturated sodium bicarbonate
solution (100 mL), and the layers were separated. The organic layer was washed
with 10% citric acid solution (50 mL) and brine (50 mL) the layers were separated

and the organic layer dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was triturated with ethyl ether/ethyl acetate to give 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid prop-2-ynylamide, 49 mg (28%). MS (APCI+), m/z (%): 354.2(15), 273.2 (20).

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EXAMPLE 41

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-2-ylmethyl)-amide

The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (134 mg, 0.42 mmol) was dissolved in dimethylformamide (6 mL). Added were 2-methyl-6-aminomethyl pyridine (55 mg, 45 mmol), 1-hydroxybenzotriazole hydrate (57 mg, 0.42 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (84 mg, 0.44 mmol). The mixture was stirred overnight at room temperature. The reaction mixture was concentrated on the rotary evaporator at 58°C. The residue was partitioned between ethyl acetate (200 mL) and water (100 mL), and the layers were separated. The organic layer was washed with saturated sodium bicarbonate solution (100 mL) and brine (50 mL), the layers were separated, and the organic layer dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was triturated with hexanes/ethyl acetate to give 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (6-methyl-pyridin-2-ylmethyl)-amide, 119 mg (67 %). MS (APCI+), m/z (%): 421.2(100).

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EXAMPLE 42

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2,1,3-benzothiadiazol-5-ylmethyl)-amide

The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (164 mg, 0.52 mmol) was dissolved in dimethylformamide (6 mL). Added were C-benzo[1,2,5]thiadiazol-5-yl-methyl amine hydrochloride (104 mg, 52 mmol), 1-hydroxybenzotriazole hydrate (71 mg, 0.53 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (104 mg,

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0.52 mmol). The mixture was stirred overnight at room temperature. The reaction mixture was concentrated on the rotary evaporator at 58°C. The residue was partitioned between ethyl acetate (200 mL) and water (100 mL), and the layers were separated. The organic layer was washed with saturated sodium bicarbonate solution (100 mL) and brine (50 mL), the layers were separated, and the organic layer dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was triturated with ethyl ether/ethyl acetate to give 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2,1,3-benzothiadiazol-5-ylmethyl)-amide, 169 mg (70%). MS (APCI+), m/z (%):

EXAMPLE 43

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-difluoro-benzylamide

The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (105 mg, 0.33 mmol) was dissolved in dimethylformamide (3 mL). Added were 3,4-difluorobenzyl amine (50 mg, 35 mmol), 1-hydroxybenzotriazole hydrate (45 mg, 0.33 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (66 mg, 0.35 mmol). The mixture was stirred overnight at room temperature. The reaction mixture was concentrated on the rotary evaporator. The residue was partitioned between ethyl acetate (200 mL) and water (100 mL), and the layers were separated. The organic layer was washed with saturated sodium bicarbonate solution (50 mL) and brine (50 mL), the layers were separated and the organic layer dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was triturated with hexanes/ethyl acetate to give 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3,4-difluorobenzylamide, 105 mg (72%). MS (APCI+), m/z (%): 442.1(100), 273.1 (100).

EXAMPLES 44 and 44a

6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide (Example 44)

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide hydrochloride (Example 44a)

The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (156 mg, 0.49 mmol) was dissolved in dimethylformamide (4 mL). Added were 3-aminomethylpyridine (74 mg, 69 mmol), 1-hydroxybenzotriazole hydrate (71 mg, 0.53 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (99 mg, 0.52 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was partitioned between ethyl acetate (300 mL) and water (100 mL), and the layers were separated. The organic layer was washed with saturated sodium bicarbonate solution, the layers were separated and the organic layer dried over magnesium sulfate, filtered, and evaporated in vacuo. The resulting oil began to crystallize on standing. The oil/solid was taken up in ethyl acetate, filtered, concentrated to dryness, and triturated with hexanes/ethyl acetate. The resulting solid, 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-3-ylmethyl)-amide (Example 44) was collected by filtration, 140 mg (70%). The oil from the concentrated mother liquors was taken up in tetrahydrofuran and treated with HCl gas in ethyl ether to give the hydrochloride, 35 mg (Example 44a) (7.9%). MS (APCI+), m/z (%): 407.2(100), 273.1 (50).

EXAMPLE 45

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (piperidin-4-ylmethyl)-amide hydrochloride

Step A: The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (157 mg, 0.50 mmol) was dissolved in dimethylformamide (3 mL). Added were 4-aminomethyl-N-tert-butyloxycarbonylpiperidine (113 mg, 53 mmol), 1-hydroxybenzotriazole hydrate (71 mg, 0.53 mmol) and

1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (105 mg, 0.55 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was partitioned between ethyl acetate (200 mL) and water (100 mL), and the layers were separated. The organic layer was washed with
5 saturated sodium bicarbonate solution (100 mL), the layers were separated, and the organic layer dried over magnesium sulfate, filtered, and evaporated in vacuo. The resulting oil slowly crystallized on standing. This was used directly in the next step. MS (APCI+), m/z (%): 513.3(1), 457.3 (15), 413.3 (40).

Step B: The product of Example 45, Step A, 230 mg, 45 mmol, was taken
10 up in dichloromethane (20 mL), and HCl gas was bubbled in for about 2 minutes, and the flask was stoppered and allowed to stand overnight at room temperature. The reaction mixture was concentrated to a foam, and ethyl ether was added. The resulting solid was collected by filtration. The solid was very hygroscopic and turned to a gum that solidified on standing, 6-benzyl-8-methyl-5,7-dioxo-
15 6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (piperidin-4-ylmethyl)-amide hydrochloride, 116 mg (56%); MS (APCI+), m/z (%): 413.3 (100).

EXAMPLE 46

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-fluoro-4-methoxy-benzylamide

The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (158 mg, 0.50 mmol) was dissolved in dimethylformamide (4.5 mL). Added were 3-fluoro-4-methoxybenzyl amine (80 mg, 52 mmol), 1-hydroxybenzotriazole hydrate (71 mg, 0.53 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (102 mg, 0.53 mmol). The reaction mixture was stirred 3 days at room temperature. The reaction mixture was partitioned between ethyl acetate (200 mL) and water (100 mL), and the layers were separated. The organic layer was washed with saturated sodium bicarbonate solution (100 mL), the layers were separated, and the organic layer dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was filtered through silica gel (70-230 mesh) using hexanes/ethyl acetate, 7:3, v/v, as eluant. The product-containing fractions

were concentrated and the residue triturated with ethyl ether. The resulting solid, 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-fluoro-4-methoxy-benzylamide, was collected by filtration, 53 mg (23%). MS (APCI+), m/z (%): 454.2 (80), 273.2 (100).

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EXAMPLE 47

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-2-ylmethyl)-amide hydrochloride

Step A: The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (183 mg, 0.58 mmol) was dissolved in tetrahydrofuran (30 mL). The reaction mixture was cooled to 0°C, 2 drops of dimethylformamide were added, then oxalyl chloride (0.2 mL, 2.29 mmol) was added, and the mixture was stirred at 0°C under an atmosphere of nitrogen gas for 10 minutes. Then the reaction mixture was allowed to warm to room temperature, stirred ten minutes, and then concentrated to an oil/solid without heating. This material was used directly in the next step.

Step B: To the product from Example 47, Step A, (146 mg, 0.44 mmol), was added under a nitrogen atmosphere, 2-aminomethyl pyridine (68 mg, 0.63 mmol) in pyridine (3 mL). The reaction mixture was stirred 30 minutes, and then water was added, and the resulting mixture was extracted with ethyl acetate. The ethyl acetate solution was washed with water and brine and dried over magnesium sulfate, filtered, and concentrated to an oil. Water was added to the oil and decanted. The oil was taken up in tetrahydrofuran and dried over magnesium sulfate. The process of washing with water and drying was repeated twice more to remove pyridine. The resulting brown solid was chromatographed on silica gel (70-230 mesh) using ethyl acetate as eluant. The product-containing fractions were concentrated, the residue triturated with hexanes/ethyl acetate to give an off-white solid. The solid was taken up in tetrahydrofuran and treated with HCl gas in ethyl ether. The resulting solid was collected by filtration, 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-2-ylmethyl)-amide hydrochloride, 73 mg (44%). MS (APCI+), m/z (%): 407.1 (100), 331.1 (50).

EXAMPLE 48

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methyl-benzylamide

The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (158 mg, 0.50 mmol) was dissolved in dimethylformamide (4 mL). Added were 4-methylbenzyl amine (61 mg, 50 mmol), 1-hydroxybenzotriazole hydrate (68 mg, 0.50 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (100 mg, 0.52 mmol). The mixture was stirred overnight at room temperature. The reaction mixture was concentrated on the rotary evaporator. The residue was partitioned between ethyl acetate and water. The layers were separated, and the organic layer was washed with saturated sodium bicarbonate solution, the layers were separated, and the organic layer dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was triturated with hexanes/ethyl acetate to give the product, 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methyl-benzylamide, 141 mg (67%). MS (APCI+), m/z (%): 420.2 (100).

EXAMPLE 49

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-trifluoromethyl-benzylamide

The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (158 mg, 0.50 mmol) was dissolved in dimethylformamide (4 mL). Added were 4-trifluoromethylbenzyl amine (88 mg, 50 mmol), 1-hydroxybenzotriazole hydrate (68 mg, 0.50 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (100 mg, 0.52 mmol). The mixture was stirred overnight at room temperature. The reaction mixture was concentrated on the rotary evaporator. The residue was partitioned between ethyl acetate and water. The layers were separated and the organic layer was washed with saturated sodium bicarbonate solution, the layers were separated, and the organic layer dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was triturated with hexanes/ethyl acetate to give the product, 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-

2-carboxylic acid 4-trifluoromethyl-benzylamide, 154 mg (65 %). MS (APCI+), m/z (%): 474.2 (100), 371.3 (30).

EXAMPLE 50

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-

2-carboxylic acid 4-chloro-benzylamide

The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (158 mg, 0.50 mmol) was dissolved in dimethylformamide (4 mL). Added were 4-chlorobenzyl amine (71 mg, 50 mmol), 1-hydroxybenzotriazole hydrate (68 mg, 0.50 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (100 mg, 0.52 mmol). The mixture was stirred overnight at room temperature. The reaction mixture was concentrated on the rotary evaporator. The residue was partitioned between ethyl acetate and water. The layers were separated, and the organic layer was washed with saturated sodium bicarbonate solution; the layers were separated and the organic layer dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was triturated with hexanes/ethyl acetate to give the product, 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-chloro-benzylamide; 170 mg (77%). MS (APCI+), m/z (%): 440.1 (100), 442.1 (50).

EXAMPLE 51

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-

2-carboxylic acid 4-trifluoromethoxy-benzylamide

The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (158 mg, 0.50 mmol) was dissolved in dimethylformamide (4 mL). Added were 4-trifluormethoxybenzyl amine (96 mg, 50 mmol), 1-hydroxybenzotriazole hydrate (68 mg, 0.50 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (100 mg, 0.52 mmol). The mixture was stirred overnight at room temperature. The reaction mixture was concentrated on the rotary evaporator. The residue was partitioned between ethyl acetate and water. The layers were separated, and the organic layer was washed with saturated

sodium bicarbonate solution. The layers were separated and the organic layer dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was triturated with hexanes/ethyl acetate to give the product, 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-trifluoromethoxy-benzylamide; 191 mg (80%). MS (APCI+), m/z (%): 490.2 (100), 273.2 (50).

EXAMPLE 52

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-thiazol-4-ylmethyl)-amide hydrochloride

10 **C-(2-Methyl-thiazol-4-yl)-methylamine**

Step A: C-(2-Methyl-thiazol-4-yl)-methylamine was made from 4-chloromethyl-2-methyl-thiazole in 2 steps using the procedure of Culbertson TP, Domagala JM, Peterson P, Bongers S, Nichols JB; *J. Heterocyclic Chemistry* 1987, 24, 1509.

15 **6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-thiazol-4-ylmethyl)-amide hydrochloride**

Step B: 6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid was treated as in Example 35, Step B with C-(2-Methyl-thiazol-4-yl)-methylamine. The free base crystallized from ethyl acetate. The HCl salt made as in Example 35, Step B gave 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methyl-thiazol-4-ylmethyl)-amide hydrochloride (45%); MS (APCI+), m/z (%): 427(100), 169(25).

EXAMPLE 53

25 **8-Methyl-thiazolo[3,2-c]pyrimidine-5,7-dione**

The product of Example 2, Step D, namely 6-benzyl-8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione (1.00 g, 3.67 mmol) was dissolved in benzene (25 mL). Aluminum chloride (2.00 g, 15 mmol) was added, and the mixture heated at reflux for 16 hours. The warm mixture was poured over ice and stirred until the ice melted. The resulting yellow solid was filtered and rinsed with water.

The solid was triturated with diethyl ether then dried in vacuo at 50°C for 16 hours to give 8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione (83%). mp >230°C. MS (APCI+), m/z (%): 183(100), 140(20).

EXAMPLE 54

5 **8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid**

The product from Example 3, Step A, namely 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid methyl ester (4.0 g, 12 mmol) was dissolved in benzene (115 mL). Aluminum chloride (6.4 g, 48 mmol) was added and the suspension heated at reflux for 21 hours. The warm mixture was poured over ice and stirred until the ice melted. The solid was filtered. The solid was suspended in water and 1 M sodium hydroxide (1.1 eq.) was added. The mixture was stirred for 90 minutes, then filtered. The filtrate was treated with 1 M hydrochloric acid (1.1 eq.). The resulting solid was isolated and dried in vacuo at 50°C to give 8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (99%). mp >205° C. MS (APCI+), m/z (%): 227(25), 183(100), 139(20).

EXAMPLE 55

20 **4-[2-(4-Methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid**

8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide

Step A: The product of Example 54 (10.0 g, 41 mmol) was dissolved in dimethylformamide (300 mL). To the solution was added 1-hydroxybenzotriazole hydrate (6.08 g, 45 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (10.2 g, 53 mmol), then 4-methoxybenzylamine (5.9 mL, 45 mmol). The mixture was stirred for 22 hours at room temperature. The dimethylformamide was removed in vacuum at 60°C. The residue was stirred in water for 30 minutes then filtered. The resulting solid was stirred with 10% aqueous sodium carbonate for 30 minutes. The mixture was filtered and rinsed

with water, then vacuum dried at 45°C for 16 hours to give 8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxybenzylamide (77%). MS (APCI+), m/z (%): 346(100), 303(30), 277(45).

4-Methylbenzoic acid tert-butyl ester

5 Step B: To a solution of pyridine (125 mL) and tert-butanol (125 mL, 1.31 mole) was added 4-methylbenzoyl chloride (171 mL, 1.29 mole). The reaction was stirred at room temperature for 88 hours, then poured into water (325 mL) and EtOAc (325 mL). The layers were separated. The EtOAc layer was washed with 0.5 M HCl (3 × 200 mL), water (200 mL), aqueous sodium
10 bicarbonate, and brine. The solvent was evaporated in vacuo to give the crude ester. The material was dissolved in hexanes (250 mL) and passed through silica gel eluting with additional hexanes. The solvent was evaporated in vacuo to give 4-methylbenzoic acid tert-butyl ester (96%). $^1\text{H-NMR}$ (CDCl_3) δ 7.87 (d, 2H), 7.20(d, 2H), 2.39(s, 3H), 1.58(s, 9H).

15 **4-Bromomethylbenzoic acid tert-butyl ester**

Step C: The product from Example 55, Step B (50.0 g, 0.26 mole) was dissolved in carbon tetrachloride (250 mL). N-Bromosuccinimide (46.3 g, 0.26 mole) was added followed by benzoyl peroxide (0.6 g, 0.0026 mole). The mixture was heated at reflux for 4 hours. The cooled reaction was filtered, rinsing 20 the solid with hexanes. The combined filtrate was washed with aqueous sodium bisulfite, and 0.5 M sodium hydroxide. The organic layer was dried (Na_2SO_4) and passed through silica gel eluting with hexanes. The solvent was removed in vacuo to give 4-bromomethylbenzoic acid tert-butyl ester (72%). The material could be crystallized from methanol; mp 46-48; $^1\text{H-NMR}$ (CDCl_3) δ 7.95(d, 2H), 7.41(d, 2H), 4.50(s, 2H), 1.59(s, 9H).

4-[2-(4-Methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid tert-butyl ester

Step D: The product from Example 55, Step A (10.0 g, 29.0 mmol) was suspended in dimethylformamide (300 mL). Cesium carbonate (9.55 g,

29.3 mmol) was added followed by the product of Example 55, Step C, namely 4-Bromomethylbenzoic acid tert-butyl ester (7.86 g, 29.0 mmol). After 17 hours, the dimethylformamide was removed in a vacuum at 70°C. The residue was mixed with tetrahydrofuran and filtered through a pad of Celite over silica gel eluting with additional tetrahydrofuran. The filtrate was evaporated in vacuo to an oil. The material was purified by chromatography on silica gel, eluting with CH₂Cl₂:tetrahydrofuran (19:1) to give 4-[2-(4-methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid tert-butyl ester (80%). MS (APCI+), m/z (%): 536(35), 480(100), 317(80).

10 **4-[2-(4-Methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid**

Step E: The product from Example 55, Step D (12.2 g, 22.8 mmol) was dissolved in trifluoroacetic acid (100 mL) and stirred at room temperature for 1.5 hours. The solvent was removed in vacuo at 40°C. The resulting oil crystallized in tetrahydrofuran. The tetrahydrofuran was evaporated in vacuo. The solid was triturated with diethyl ether, then vacuum dried at 45°C to give 4-[2-(4-methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid (80%); mp >210° C; MS (APCI+), m/z (%): 480(10), 317(100).

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EXAMPLE 56

4-[2-(4-Methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid sodium salt

To the product of Example 55, Step E (1.05 g, 2.19 mmol), suspended in ethanol (120 mL) was added 1 M sodium hydroxide (2.23 mL, 2.23 mmol). After 25 20 minutes, water (2 mL) was added to complete the solution. The solution was filtered and the filtrate evaporated to a white solid. The material was triturated with ethanol (10 mL) and rinsed twice with diethyl ether. The solid was vacuum dried at 55°C for 18 hours to give 4-[2-(4-methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid sodium salt (95%); MS (APCI+), m/z (%): 480(20), 317(100).

EXAMPLE 57

4-[2-(4-Methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester hydrochloride

The product of Example 55, Step E was treated as in the procedure of Example 55, Step A using N,N-dimethylaminoethanol. The crude product was dissolved in ethyl acetate/tetrahydrofuran and washed with water, 10% aqueous sodium carbonate and brine, dried (Na_2SO_4) and evaporated to the free base. The material was dissolved in tetrahydrofuran and treated with 1 M HCl in diethyl ether (1.2 equivalents). The resulting solid was filtered and rinsed with diethyl ether, then vacuum dried to give 4-[2-(4-methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester hydrochloride (67%); MS (APCI+), m/z (%): 551(100), 317 (30).

EXAMPLE 58

4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid

8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

Step A: 8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid was treated as in Example 55, Step A using 4-fluoro-benzylamine to give 8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide (99%); MS (APCI+), m/z (%): 334(100), 291(50), 265(95).

25 4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid tert-butyl ester

Step B: The product of Step A was treated as in Example 55, Step D to give 4-[2-(4-fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid tert-butyl ester (63%); MS (APCI+), m/z (%): 524(35), 468(100), 317(55).

4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid

Step C: The product from Step B was treated as in Example 55, Step E to give 4-[2-(4-fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid (93%); MS (APCI+), m/z (%): 468(100), 317(50).

EXAMPLE 59

4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid Sodium Salt

4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid was treated as in Example 56 to give 4-[2-(4-fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid sodium salt (85%); MS (APCI+), m/z (%): 468(30), 317 (100).

EXAMPLE 60

4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester

4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid was treated with N,N-dimethylaminoethanol as in Example 57. The crude compound was dissolved in ethyl acetate and washed with water and 10% aqueous sodium carbonate, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel eluting with $\text{CH}_2\text{Cl}_2:\text{MeOH}$ 9:1 to give 4-[2-(4-fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester (30%); MS (APCI+), m/z (%): 539(100), 388(15), 317(20).

EXAMPLE 61

4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester hydrochloride

The product of Example 60 was dissolved in tetrahydrofuran and treated with 1 M HCl in diethyl ether (1.2 equivalents). The resulting solid was filtered and rinsed with diethyl ether, then vacuum dried to give 4-[2-(4-fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid 2-dimethylamino-ethyl ester hydrochloride (41%); MS (APCI+), m/z (%): 539(100), 388(20), 317(40).

EXAMPLE 62

4-{8-Methyl-5,7-dioxo-2-[(pyridin-4-ylmethyl)-carbamoyl]-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid trifluoro-acetate

8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide

Step A: 8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid was treated as in Example 55, Step A using C-pyridin-4-yl-methylamine to give 8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide (82%); MS (APCI+), m/z (%): 317(100), 274(50), 248(95).

4-{8-Methyl-5,7-dioxo-2-[(pyridin-4-ylmethyl)-carbamoyl]-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid tert-butyl ester

Step B: The product of Step A was treated as in Example 55, Step D to give 4-{8-methyl-5,7-dioxo-2-[(pyridin-4-ylmethyl)-carbamoyl]-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid tert-butyl ester (47%); MS (AP+) m/z (%): 507(100), 451(35), 317(35), 147(40).

4-{8-Methyl-5,7-dioxo-2-[(pyridin-4-ylmethyl)-carbamoyl]-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid trifluoro-acetate

Step C: The product from Step B was treated as in Example 55, Step E. Trituration with diethyl ether, ethyl acetate and again with diethyl ether gave
5 4-(8-methyl-5,7-dioxo-2-[(pyridin-4-ylmethyl)-carbamoyl]-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid trifluoro-acetate (93%); MS (APCI+), m/z (%): 451(40), 317(100), 135(30).

EXAMPLE 63

4-{8-Methyl-5,7-dioxo-2-[(pyridin-4-ylmethyl)-carbamoyl]-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid 2-dimethylamino-ethyl ester dihydrochloride

4-{8-Methyl-5,7-dioxo-2-[(pyridin-4-ylmethyl)-carbamoyl]-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid trifluoro-acetate was treated as in Example 57. The crude product was dissolved in water and sodium bicarbonate was added until pH 8. The aqueous layer was extracted with ethyl acetate and ethyl acetate/tetrahydrofuran. The combined organic layers were washed with water, 10% sodium carbonate, and brine then evaporated to a foam. The material 15 was chromatographed on silica gel eluting with tetrahydrofuran to give the free base. The foam was dissolved in tetrahydrofuran and treated with 1 M HCl in diethyl ether (2.06 eq.) to give 4-{8-methyl-5,7-dioxo-2-[(pyridin-4-ylmethyl)-20 carbamoyl]-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl}-benzoic acid 2-dimethylamino-ethyl ester dihydrochloride (93%); MS (APCI+), m/z (%): 522(100), 388(20), 317(40), 135(20).

EXAMPLE 64

8-Methyl-6-(2-methyl-thiazol-4-ylmethyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide was treated as in Example 55, Step D with 2-methyl-4-bromomethyl-thiazole. The crude product was chromatographed 30 with silica gel eluting with CH₂Cl₂:tetrahydrofuran 9:1 to give 8-methyl-6-(2-methyl-thiazol-4-ylmethyl)-5,7-dioxo-6,7-dihydro-5H-

thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide (37%); MS (APCI+), m/z (%): 445(100), 294(80).

EXAMPLE 65

5 **2-Chloro-4-[2-(4-fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester**

10 8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide was treated as in Example 55, Step D with 4-bromomethyl-2-chloro-benzoic acid methyl ester. The crude product was chromatographed on silica gel eluting with CH₂Cl₂:tetrahydrofuran 9:1, then triturated with diethyl ether to give 2-chloro-4-[2-(4-fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester (86%); mp 176-178°C; MS (APCI+), m/z (%): 518(40), 516(100), 367(20), 365(50).

EXAMPLE 66

15 **8-Methyl-5,7-dioxo-6-(2H-tetrazol-5-ylmethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide**

8-Methyl-5,7-dioxo-6-[(2-triphenylmethyl)-2H-tetrazol-5-ylmethyl]-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluorobenzylamide

Step A: 8-Methyl-5,7-dioxo-6,7-dihydro-5*H*-thiazolo[3,2-*c*]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide was treated as in Example 55, Step D with 5-chloromethyl-2-(triphenylmethyl)-2*H*-tetrazole. The crude product was chromatographed on silica gel eluting with CH₂Cl₂:tetrahydrofuran, 19:1 to give 8-methyl-5,7-dioxo-6-[(2-triphenylmethyl)-2*H*-tetrazol-5-ylmethyl]-6,7-dihydro-5*H*-thiazolo[3,2-*c*]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide (50%); ¹H-NMR (DMSO-*d*₆) δ 9.32(t, 1H), 7.36(m, 11H), 7.16(t, 2H), 6.95(m, 6H), 5.34(s, 2H), 4.39(s, 2H), 1.88(s, 3H).

8-Methyl-5,7-dioxo-6-(2H-tetrazol-5-ylmethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

Step B: The product from Example 66, Step A (295 mg, 0.45 mmol) was suspended in trifluoroacetic acid (5.0 mL). Triethylsilane was added dropwise until the mixture became colorless. The solvent was evapoarated in vacuo, and the residue triturated twice with diethyl ether. The material was vacuum dried at room temperature to give 8-methyl-5,7-dioxo-6-(2H-tetrazol-5-ylmethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide (53%); MS (APCI+), m/z (%): 416(35), 373(25), 306(30), 265(95), 222(100), 209(20).

10

EXAMPLE 67

8-Methyl-5,7-dioxo-6-thiazol-2-ylmethyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide hydrochloride

15

8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide was treated as in Example 55, Step D with 4-chloromethyl-thiazole. The crude product was chromatographed on silica gel eluting with CH_2Cl_2 :tetrahydrofuran, 5:1. The resulting free base was dissolved in tetrahydrofuran and treated with 1M HCl in diethyl ether (1.2 eq.) and stirred 30 minutes. The solid was isolated by filtration and dried in vacuo at room temperature to give 8-methyl-5,7-dioxo-6-thiazol-2-ylmethyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide hydrochloride (44%); mp 183-185° C; MS (APCI+), m/z (%): 431(100), 280(20).

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EXAMPLE 68

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4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-2-methyl-benzoic acid methyl ester

30

8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide was treated as in Example 55, Step D with 4-bromomethyl-2-methyl-benzoic acid methyl ester. The crude product was chromatographed on silica gel eluting with CH_2Cl_2 :tetrahydrofuran 9:1, then triturated with diethyl ether to give 4-[2-(4-fluoro-benzylcarbamoyl)-8-methyl-

5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-2-methyl-benzoic acid methyl ester (75%); mp 179-180° C; MS (APCI+), m/z (%): 496(100), 345(15).

EXAMPLE 69

5 **4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-2-methoxy-benzoic acid methyl ester**
8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide was treated as in Example 55, Step D with 4-bromomethyl-2-methoxy-benzoic acid methyl ester. The crude product was chromatographed on silica gel eluting with CH₂Cl₂:tetrahydrofuran 19:1, then
10 crystallized from diethyl ether and vacuum dried at room temperature to give
4-[2-(4-fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-2-methoxy-benzoic acid methyl ester (75%); mp 191-193° C; MS (APCI+), m/z (%): 512(100), 361(10).

EXAMPLE 70

15 **6-(4-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride**
8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide was treated as in Example 55, Step D with 4-fluorobenzyl bromide. The crude product was chromatographed on silica gel eluting with CH₂Cl₂:tetrahydrofuran 2:1. The isolated free base was dissolved in tetrahydrofuran and treated with 1M HCl in diethyl ether to give
20 6-(4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride (48%); MS (APCI+), m/z (%): 425(100), 291(40), 257(20).

EXAMPLE 71

6-(4-Bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride

8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide was treated as in Example 55, Step D with 4-bromobenzyl bromide. The crude product was chromatographed on silica gel eluting with CH_2Cl_2 :tetrahydrofuran, 2:1. The isolated free base was dissolved in tetrahydrofuran and treated with 1M HCl in diethyl ether to give 6-(4-bromo-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride (48%); MS (APCI+), m/z (%): 487(100), 485(100).

EXAMPLE 72

6-(4-Chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide

8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide was treated as in Example 55, Step D with 4-chlorobenzyl bromide. The crude product was chromatographed on silica gel eluting with CH_2Cl_2 :tetrahydrofuran, 2:1. The isolated free base was dissolved in tetrahydrofuran and treated with 1M HCl in diethyl ether to give 6-(4-chloro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride (65%); MS (APCI+), m/z (%): 441(100), 307(20).

EXAMPLE 73

8-Methyl-6-[4-(morpholine-4-carbonyl)-benzyl]-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride

8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide was treated as in Example 55, Step D with 1-(4-bromomethylphenyl)-1-morpholin-4-ylmethanone. The crude product was triturated with ethyl acetate to give the free base. The isolated free

base was dissolved in tetrahydrofuran and treated with 1*M* HCl in diethyl ether to give 8-methyl-6-[4-(morpholine-4-carbonyl)-benzyl]-5,7-dioxo-6,7-dihydro-5*H*-thiazolo[3,2-*c*]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride (56%); MS (APCI+), m/z (%): 520(80), 392(100), 336(70),
5 292(80).

EXAMPLE 74

{5-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7*H*-thiazolo[3,2-*c*]pyrimidin-6-ylmethyl]-isoxazol-3-yl}-carbamic acid methyl ester

10 8-Methyl-5,7-dioxo-6,7-dihydro-5*H*-thiazolo[3,2-*c*]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide (100 mg, 0.3 mmol) was dissolved in dimethylformamide (3 mL), and cesium carbonate (98 mg, 0.3 mmol) was added, then (5-bromomethyl-isoxazol-3-yl)-carbamic acid methyl ester (71 mg, 0.30 mmol) was added and the mixture stirred overnight at room temperature. The reaction mixture was partitioned between ethyl acetate and 10% citric acid solution, the layers separated, the organic layer washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel (70-230 mesh) using hexanes/ethyl acetate, 1:1, v/v, then 1/2, v/v as eluant to give the product, {5-[2-(4-fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7*H*-thiazolo[3,2-*c*]pyrimidin-6-ylmethyl]-isoxazol-3-yl}-carbamic acid methyl ester, 58 mg (40%). MS (APCI+), m/z (%): 488.1(100), 265.2(98).
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EXAMPLE 75

8-Methyl-5,7-dioxo-6-[4-(2*H*-tetrazol-5-yl)-benzyl]-6,7-dihydro-5*H*-thiazolo[3,2-*c*]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

25 Step A: 8-Methyl-5,7-dioxo-6,7-dihydro-5*H*-thiazolo[3,2-*c*]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide (200 mg, 0.6 mmol) was dissolved in dimethylformamide (5 mL), and cesium carbonate (196 mg, 0.6 mmol) was added; then (4-bromomethyl-phenyl)-trityl-2*H* -tetrazole (289 mg, 0.6 mmol) was added and the mixture stirred over three days at room temperature. The reaction mixture was partitioned between ethyl acetate and 10% citric acid solution, the aqueous layer back-extracted, the organic layers combined, the organic layer

washed with 10% citric acid and three times with brine, dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed on silica gel (70-230 mesh) using hexanes/ethyl acetate, 2:1, v/v, then 1:1, v/v as eluant to give the product, which was used directly in the next step, 186 mg (42%). MS
5 (APCI+), m/z (%): 678.3(10), 243.2(100).

Step B: The product from Step A, (186 mg, 0.25 mmol) was taken up in trifluoroacetic acid (6 mL) at room temperature and stirred for 3 hours. The reaction mixture was concentrated to dryness, and water was added and a white precipitate formed and was collected by filtration and washed with ethyl ether and
10 hexanes to give the product, 8-methyl-5,7-dioxo-6-[4-(2H-tetrazol-5-yl)-benzyl]-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide, 80 mg (65%). MS (APCI+), m/z (%): 492.2(60).

EXAMPLE 76

15 8-Methyl-6-[4-(morpholine-4-carbonyl)-benzyl]-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide (150 mg, 0.45 mmol) was dissolved in dimethylformamide (4 mL), and cesium carbonate (148 mg, 0.45 mmol) was added and then 1-(4-bromomethyl-phenyl)-1-morpholino-4-ylmethanone (128 mg,
20 0.45 mmol) was added and the mixture stirred four days at room temperature. The dimethylformamide was removed in vacuo. The residue was partitioned between ethyl acetate and 10% citric acid solution, the layers separated, the organic layer washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was triturated with hexanes/ethyl acetate to give the product, 8-methyl-
25 6-[4-(morpholine-4-carbonyl)-benzyl]-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide), 143 mg (59%). MS (APCI+), m/z (%): 537.2(50), 386.2 (100).

EXAMPLE 77

6-(6-Fluoro-quinolin-2-ylmethyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-

5 2-carboxylic acid 4-fluoro-benzylamide (150 mg, 0.45 mmol) was dissolved in dimethylformamide (4 mL) and cesium carbonate (148 mg, 0.45 mmol) was added and then 2-(chloromethyl)-6-fluoro-quinoline (88 mg, 0.45 mmol) was added and the mixture stirred 4 days at room temperature. The dimethylformamide was removed in vacuo. The residue was partitioned between ethyl acetate and water, the layers separated, the organic layer washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was triturated with hexanes/ethyl acetate to give the product, 6-(6-fluoro-quinolin-2-ylmethyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide, 143 mg (64%). MS (APCI+), m/z (%):

10 493.2(50), 342.2 (100).

EXAMPLE 78

2-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-5-methoxy-pyrimidine-4-carboxylic acid methyl ester

20 8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide (150 mg, 0.45 mmol) was dissolved in dimethylformamide (4 mL) and cesium carbonate (148 mg, 0.45 mmol) was added and then 2-chloromethyl-5-methoxy-pyrimidine-4-carboxylic acid methyl ester (117 mg, 0.45 mmol) was added, and the mixture stirred 4 days at room temperature. The dimethylformamide was removed in vacuo. The residue was partitioned between ethyl acetate and water, the layers separated, the organic layer washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was triturated with hexanes/ethyl acetate to give the product,

25 2-[2-(4-fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-5-methoxy-pyrimidine-4-carboxylic acid methyl ester, 30 mg (13%). MS (APCI+), m/z (%): 514.2(100), 363.2 (50).

EXAMPLE 79

6-But-2-ynyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-

5 2-carboxylic acid 4-fluoro-benzylamide (150 mg, 0.45 mmol) was dissolved in dimethylformamide (4 mL) and cesium carbonate (148 mg, 0.45 mmol) was added, and then 1-bromo-2-butyne (60 mg, 0.45 mmol) was added and the mixture stirred 5 days at room temperature. The dimethylformamide was removed in vacuo. The residue was partitioned between ethyl acetate and 10% citric acid
10 solution, the layers separated, the organic layer washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was triturated with hexanes/ethyl acetate to give the product, 6-but-2-ynyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide, 125 mg (72%). MS (APCI+), m/z (%): 386.2(100).

EXAMPLE 80

8-Methyl-5,7-dioxo-6-(2-oxo-2H-1-benzopyran-6-ylmethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-

20 2-carboxylic acid 4-fluoro-benzylamide (377 mg, 1.1 mmol) was dissolved in dimethylformamide (7 mL) and cesium carbonate (365 mg, 1.1 mmol) was added, and then 6-bromomethyl-chromen-2-one (270 mg, 1.1 mmol) was added and the mixture stirred 13 days at room temperature. The dimethylformamide was removed in vacuo. The residue was partitioned between ethyl acetate and 10% citric acid solution, the layers separated, the organic layer washed with 10% citric acid and brine, dried over magnesium sulfate, filtered and concentrated. The residue was triturated with hexanes/ethyl acetate and then chromatographed on a short pad of silica gel (70-230 mesh) followed by column chromatography using hexanes/ethyl acetate to give the product, 8-methyl-5,7-dioxo-6-(2-oxo-2H-1-benzopyran-6-ylmethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-
25 2-carboxylic acid 4-fluoro-benzylamide, 78 mg (14%). MS (APCI+), m/z (%): 492.3(100), 341.1 (80).

EXAMPLE 81

6-(4-Methanesulfonyl-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride

The product from Example 62, Step A, namely 8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide (158 mg, 0.5 mmol) was dissolved in dimethylformamide (5 mL), and cesium carbonate (163 mg, 0.5 mmol) was added followed by 4-methanesulfonylbenzyl chloride (102 mg, 0.5 mmol), and the mixture stirred overnight at room temperature. The dimethylformamide was removed in vacuo. The residue was partitioned between ethyl acetate and water, the layers separated, the organic layer washed with brine, dried over magnesium sulfate, filtered and concentrated. No product was in the ethyl acetate layer. The product was insoluble in both phases. The insoluble material was collected by filtration and dried in vacuo. The solid was stirred in ethereal HCl to give the product, 6-(4-methanesulfonyl-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride, 0.082 g (32%). MS (APCI+), m/z (%): 485.1(100), 351.0 (50).

EXAMPLE 82

6-(3-Cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride

The product from Example 62, Step A, namely 8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide (158 mg, 0.5 mmol) was dissolved in dimethylformamide (5 mL) and cesium carbonate (163 mg, 0.5 mmol) was added and then 3-cyanobenzyl bromide (98 mg, 0.5 mmol) was added, and the mixture stirred overnight at room temperature. The dimethylformamide was removed in vacuo. The residue was partitioned between ethyl acetate and water, the layers separated, the organic layer washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was triturated with hexanes/ethyl acetate to give the product, 151 mg (70%). A portion of the solid was stirred in ethereal HCl to give the product,

2025 2030 2035 2040 2045 2050 2055 2060 2065 2070 2075 2080 2085 2090 2095 2100 2105 2110 2115 2120 2125 2130 2135 2140 2145 2150 2155 2160 2165 2170 2175 2180 2185 2190 2195 2200 2205 2210 2215 2220 2225 2230 2235 2240 2245 2250 2255 2260 2265 2270 2275 2280 2285 2290 2295 2300 2305 2310 2315 2320 2325 2330 2335 2340 2345 2350 2355 2360 2365 2370 2375 2380 2385 2390 2395 2400 2405 2410 2415 2420 2425 2430 2435 2440 2445 2450 2455 2460 2465 2470 2475 2480 2485 2490 2495 2500 2505 2510 2515 2520 2525 2530 2535 2540 2545 2550 2555 2560 2565 2570 2575 2580 2585 2590 2595 2600 2605 2610 2615 2620 2625 2630 2635 2640 2645 2650 2655 2660 2665 2670 2675 2680 2685 2690 2695 2700 2705 2710 2715 2720 2725 2730 2735 2740 2745 2750 2755 2760 2765 2770 2775 2780 2785 2790 2795 2800 2805 2810 2815 2820 2825 2830 2835 2840 2845 2850 2855 2860 2865 2870 2875 2880 2885 2890 2895 2900 2905 2910 2915 2920 2925 2930 2935 2940 2945 2950 2955 2960 2965 2970 2975 2980 2985 2990 2995 2998 3000 3002 3004 3006 3008 3010 3012 3014 3016 3018 3020 3022 3024 3026 3028 3030 3032 3034 3036 3038 3040 3042 3044 3046 3048 3050 3052 3054 3056 3058 3060 3062 3064 3066 3068 3070 3072 3074 3076 3078 3080 3082 3084 3086 3088 3090 3092 3094 3096 3098 3100 3102 3104 3106 3108 3110 3112 3114 3116 3118 3120 3122 3124 3126 3128 3130 3132 3134 3136 3138 3140 3142 3144 3146 3148 3150 3152 3154 3156 3158 3160 3162 3164 3166 3168 3170 3172 3174 3176 3178 3180 3182 3184 3186 3188 3190 3192 3194 3196 3198 3200 3202 3204 3206 3208 3210 3212 3214 3216 3218 3220 3222 3224 3226 3228 3230 3232 3234 3236 3238 3240 3242 3244 3246 3248 3250 3252 3254 3256 3258 3260 3262 3264 3266 3268 3270 3272 3274 3276 3278 3280 3282 3284 3286 3288 3290 3292 3294 3296 3298 3300 3302 3304 3306 3308 3310 3312 3314 3316 3318 3320 3322 3324 3326 3328 3330 3332 3334 3336 3338 3340 3342 3344 3346 3348 3350 3352 3354 3356 3358 3360 3362 3364 3366 3368 3370 3372 3374 3376 3378 3380 3382 3384 3386 3388 3390 3392 3394 3396 3398 3400 3402 3404 3406 3408 3410 3412 3414 3416 3418 3420 3422 3424 3426 3428 3430 3432 3434 3436 3438 3440 3442 3444 3446 3448 3450 3452 3454 3456 3458 3460 3462 3464 3466 3468 3470 3472 3474 3476 3478 3480 3482 3484 3486 3488 3490 3492 3494 3496 3498 3500 3502 3504 3506 3508 3510 3512 3514 3516 3518 3520 3522 3524 3526 3528 3530 3532 3534 3536 3538 3540 3542 3544 3546 3548 3550 3552 3554 3556 3558 3560 3562 3564 3566 3568 3570 3572 3574 3576 3578 3580 3582 3584 3586 3588 3590 3592 3594 3596 3598 3600 3602 3604 3606 3608 3610 3612 3614 3616 3618 3620 3622 3624 3626 3628 3630 3632 3634 3636 3638 3640 3642 3644 3646 3648 3650 3652 3654 3656 3658 3660 3662 3664 3666 3668 3670 3672 3674 3676 3678 3680 3682 3684 3686 3688 3690 3692 3694 3696 3698 3700 3702 3704 3706 3708 3710 3712 3714 3716 3718 3720 3722 3724 3726 3728 3730 3732 3734 3736 3738 3740 3742 3744 3746 3748 3750 3752 3754 3756 3758 3760 3762 3764 3766 3768 3770 3772 3774 3776 3778 3780 3782 3784 3786 3788 3790 3792 3794 3796 3798 3800 3802 3804 3806 3808 3810 3812 3814 3816 3818 3820 3822 3824 3826 3828 3830 3832 3834 3836 3838 3840 3842 3844 3846 3848 3850 3852 3854 3856 3858 3860 3862 3864 3866 3868 3870 3872 3874 3876 3878 3880 3882 3884 3886 3888 3890 3892 3894 3896 3898 3900 3902 3904 3906 3908 3910 3912 3914 3916 3918 3920 3922 3924 3926 3928 3930 3932 3934 3936 3938 3940 3942 3944 3946 3948 3950 3952 3954 3956 3958 3960 3962 3964 3966 3968 3970 3972 3974 3976 3978 3980 3982 3984 3986 3988 3990 3992 3994 3996 3998 3999 4000 4001 4002 4003 4004 4005 4006 4007 4008 4009 4010 4011 4012 4013 4014 4015 4016 4017 4018 4019 4020 4021 4022 4023 4024 4025 4026 4027 4028 4029 4030 4031 4032 4033 4034 4035 4036 4037 4038 4039 4040 4041 4042 4043 4044 4045 4046 4047 4048 4049 4050 4051 4052 4053 4054 4055 4056 4057 4058 4059 4060 4061 4062 4063 4064 4065 4066 4067 4068 4069 4070 4071 4072 4073 4074 4075 4076 4077 4078 4079 4080 4081 4082 4083 4084 4085 4086 4087 4088 4089 4090 4091 4092 4093 4094 4095 4096 4097 4098 4099 4100 4101 4102 4103 4104 4105 4106 4107 4108 4109 4110 4111 4112 4113 4114 4115 4116 4117 4118 4119 4120 4121 4122 4123 4124 4125 4126 4127 4128 4129 4130 4131 4132 4133 4134 4135 4136 4137 4138 4139 4140 4141 4142 4143 4144 4145 4146 4147 4148 4149 4150 4151 4152 4153 4154 4155 4156 4157 4158 4159 4160 4161 4162 4163 4164 4165 4166 4167 4168 4169 4170 4171 4172 4173 4174 4175 4176 4177 4178 4179 4180 4181 4182 4183 4184 4185 4186 4187 4188 4189 4190 4191 4192 4193 4194 4195 4196 4197 4198 4199 4200 4201 4202 4203 4204 4205 4206 4207 4208 4209 4210 4211 4212 4213 4214 4215 4216 4217 4218 4219 4220 4221 4222 4223 4224 4225 4226 4227 4228 4229 4230 4231 4232 4233 4234 4235 4236 4237 4238 4239 4240 4241 4242 4243 4244 4245 4246 4247 4248 4249 4250 4251 4252 4253 4254 4255 4256 4257 4258 4259 4260 4261 4262 4263 4264 4265 4266 4267 4268 4269 4270 4271 4272 4273 4274 4275 4276 4277 4278 4279 4280 4281 4282 4283 4284 4285 4286 4287 4288 4289 4290 4291 4292 4293 4294 4295 4296 4297 4298 4299 4300 4301 4302 4303 4304 4305 4306 4307 4308 4309 4310 4311 4312 4313 4314 4315 4316 4317 4318 4319 4320 4321 4322 4323 4324 4325 4326 4327 4328 4329 4330 4331 4332 4333 4334 4335 4336 4337 4338 4339 4340 4341 4342 4343 4344 4345 4346 4347 4348 4349 4350 4351 4352 4353 4354 4355 4356 4357 4358 4359 4360 4361 4362 4363 4364 4365 4366 4367 4368 4369 4370 4371 4372 4373 4374 4375 4376 4377 4378 4379 4380 4381 4382 4383 4384 4385 4386 4387 4388 4389 4390 4391 4392 4393 4394 4395 4396 4397 4398 4399 4400 4401 4402 4403 4404 4405 4406 4407 4408 4409 4410 4411 4412 4413 4414 4415 4416 4417 4418 4419 4420 4421 4422 4423 4424 4425 4426 4427 4428 4429 4430 4431 4432 4433 4434 4435 4436 4437 4438 4439 4440 4441 4442 4443 4444 4445 4446 4447 4448 4449 4450 4451 4452 4453 4454 4455 4456 4457 4458 4459 4460 4461 4462 4463 4464 4465 4466 4467 4468 4469 4470 4471 4472 4473 4474 4475 4476 4477 4478 4479 4480 4481 4482 4483 4484 4485 4486 4487 4488 4489 4490 4491 4492 4493 4494 4495 4496 4497 4498 4499 4500 4501 4502 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4889 4889 4890 4891 4892 4893 4894 4895 4896 4897 4898 4898 4899 4899 4900 4901 4902 4903 4904 4905 4906 4907 4908 4909 4909 4910 4911 4912 4913 4914 4915 4916 4917 4918 4919 4919 4920 4921 4922 4923 4924 4925 4926 4927 4928 4929 4929 4930 4931 4932 4933 4934 4935 4936 4937 4938 4939 4939 4940 4941 4942 4943 4944 4945 4946 4947 4948 4949 4949 4950 4951 4952 4953 4954 4955 4956 4957 4958 4959 4959 4960 4961 4962 4963 4964 4965 4966 4967 4968 4969 4969 4970 4971 4972 4973 4974 4975 4976 4977 4978 4978 4979 4979 4980 4981 4982 4983 4984 4985 4986 4987 4988 4989 4989 4990 4991 4992 4993 4994 4995 4996 4997 4998 4998 4999 4999 5000 5001 5002 5003 5004 5005 5006 5007 5008 5009 5009 5010 5011 5012 5013 5014 5015 5016 5017 5018 5019 5019 5020 5021 5022 5023 5024 5025 5026 5027 5028 5029 5029 5030 5031 5032 5033 5034 5035 5036 5037 5038 5039 5039 5040 5041 5042 5043 5044 5045 5046 5047 5048 5049 5049 5050 5051 5052 5053 5054 5055 5056 5057 5058 5059 5059 5060 5061 5062 5063 5064 5065 5066 5067 5068 5069 5069 5070 5071 5072 5073 5074 5075 5076 5077 5078 5078 5079 5079 5080 5081 5082 5083 5084 5085 5086 5087 5088 5089 5089 5090 5091 5092 5093 5094 5095 5096 5097 5098 5098 5099 5099 5100 5101 5102 5103 5104 5105 5106 5107 5108 5109 5109 5110 5111 5112 5113 5114 5115 5116 5117 5118 5119 5119 5120 5121 5122 5123 5124 5125 5126 5127 5128 5129 5129 5130 5131 5132 5133 5134 5135 5136 5137 5138 5139 5139 5140 5141 5142 5143 5144 5145 5146 5147 5148 5149 5149 5150 5151 5152 5153 5154 5155 5156 5157 5158 5159 5159 5160 5161 5162 5163 5164 5165 5166 5167 5168 5169 5169 5170 5171 5172 5173 5174 5175 5176 5177 5178 5178 5179 5179 5180 5181 5182 5183 5184 5185 5186 5187 5188 5189 5189 5190 5191 5192 5193 5194 5195 5196 5197 5198 5198 5199 5199 5200 5201 5202 5203 5204 5205 5206 5207 5208 5209 5209 5210 5211 5212 5213 5214 5215 5216 5217 5218 5219 5219 5220 5221 5222 5223 5224 5225 5226 5227 5228 5229 5229 5230 5231 5232 5233 5234 5235 5236 5237 5238 5239 5239 5240 5241 5242 5243 5244 5245 5246 5247 5248 5249 5249 5250 5251 5252 5253 5254 5255 5256 5257 5258 5259 5259 5260 5261 5262 5263 5264 5265 5266 5267 5268 5269 5269 5270 5271 5272 5273 5274 5275 5276 5277 5278 5278 5279 5279 5280 5281 5282 5283 5284 5285 5286 5287 5288 5289 5289 5290 5291 5292 5293 5294 5295 5296 5297 5298 5298 5299 5299 5300 5301 5302 5303 5304 5305 5306 5307 5308 5309 5309 5310 5311 5312 5313

6-(3-cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride, 0.082 g. MS (APCI+), m/z (%): 432.1(100), 298.1 (50).

EXAMPLE 83

5 **6-[2-(4-Chloro-benzenesulfonyl)-ethyl]-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride**

The product from Example 62, Step A, namely 8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide (158 mg, 0.5 mmol) was dissolved in dimethylformamide (5 mL), and cesium carbonate (163 mg, 0.5 mmol) was added; then 2-chloroethyl-4-chlorophenyl sulfone (120 mg, 0.5 mmol) was added, and the mixture stirred overnight at room temperature. The dimethylformamide was removed in vacuo. The residue was partitioned between ethyl acetate and water, the layers separated, the organic layer washed with brine, dried over magnesium sulfate, filtered and concentrated. The solid was stirred 2 hours in ethereal HCl to give the product, 6-[2-(4-chloro-benzenesulfonyl)-ethyl]-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride, 156 mg (57%). MS (APCI+), m/z (%): 519.1(40), 521.1 (20).

20

EXAMPLE 84

8-Methyl-5,7-dioxo-6-(4-sulfamoyl-benzyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride

The product from Example 62, Step A, namely 8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide (158 mg, 0.5 mmol) was dissolved in dimethylformamide (5 mL), and cesium carbonate (163 mg, 0.5 mmol) was added; then 4-bromomethylbenzene sulfonamide (125 mg, 0.5 mmol) was added and the mixture stirred overnight at room temperature. The dimethylformamide was removed in vacuo. The residue was partitioned between ethyl acetate and water, the layers separated, the organic layer washed with brine, dried over magnesium sulfate, filtered and concentrated.

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The solid was stirred 1 hour in ethereal HCl to give the product, 8-methyl-5,7-dioxo-6-(4-sulfamoyl-benzyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid(pyridin-4-ylmethyl)-amide hydrochloride, 145 mg (56%). MS (APCI+), m/z (%): 486.1(100), 352.0 (90).

5

EXAMPLE 85

6-(4-Cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride

The product from Example 62, Step A, namely 8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide (158 mg, 0.5 mmol) was dissolved in dimethylformamide (5 mL), and cesium carbonate (163 mg, 0.5 mmol) was added; then 4-cyanobenzyl bromide (98 mg, 0.5 mmol) was added and the mixture stirred overnight at room temperature. The dimethylformamide was removed in vacuo. The residue was partitioned between ethyl acetate and water, the layers separated, the organic layer washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was triturated with hexanes/ethyl acetate to give a pale brown solid. The solid was stirred in ethereal HCl for 1 hour to give the product, 6-(4-cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (pyridin-4-ylmethyl)-amide hydrochloride, 0.102 g. MS (AP+) m/z (%): 432.1(100), 298.0 (30).

EXAMPLE 86

8-Methyl-5,7-dioxo-6-(3-oxo-3-phenyl-propyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

In an 8 mL screw cap vial was added a solution of 8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide,(0.033 g, 0.1 mmol) in dimethylformamide (1 mL), a solution of 3-chloro-1-phenyl-propan-1-one (0.039 g, 0.23 mmol) in dimethylformamide (0.575 mL) and anhydrous cesium carbonate (0.075 g, 0.023 mmol). The vial was capped and the reaction mixture was shaken for 24 hours at room temperature. The reaction mixture was filtered and the solvent was removed under vacuum.

Purification was carried out via reverse-phase HPLC (3% n-propanol in acetonitrile and 3% n-propanol in water as the eluent; C-18 column). 0.028 g (60%). MS (APCI), m/z ([M+H]⁺) 466.5.

EXAMPLE 87

5 **8-Methyl-5,7-dioxo-6-(1-phenyl-ethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide**

The reaction was run according to the procedure of Example 86.

MS (APCI), m/z ([M+H]⁺) 438.4.

EXAMPLE 88

10 **8-Methyl-5,7-dioxo-6-(2-phenylmethanesulfonyl-ethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide**

The reaction was run according to the procedure of Example 86.

MS (APCI), m/z ([M+H]⁺) 516.5.

EXAMPLE 89

15 **6-(5-Cyano-pentyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide**

The reaction was run according to the procedure of Example 86.

MS (APCI), m/z ([M+H]⁺) 429.4.

EXAMPLE 90

20 **6-(E)-But-2-enyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide**

The reaction was run according to the procedure of Example 86.

MS (APCI), m/z ([M+H]⁺) 388.4.

EXAMPLE 91

8-Methyl-5,7-dioxo-6-(E)-pent-2-enyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

The reaction was run according to the procedure of Example 86.

5 MS (APCI), m/z ([M+H]⁺) 402.4.

EXAMPLE 92

6-sec-Butyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

The reaction was run according to the procedure of Example 86.

10 MS (APCI), m/z ([M+H]⁺) 390.4.

EXAMPLE 93

8-Methyl-6-(2-methyl-allyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

The reaction was run according to the procedure of Example 86.

15 MS (APCI), m/z ([M+H]⁺) 388.4.

EXAMPLE 94

6-(1-Ethyl-propyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

The reaction was run according to the procedure of Example 86.

20 MS (APCI), m/z ([M+H]⁺) 404.4.

EXAMPLE 95

8-Methyl-5,7-dioxo-6-pent-2-ynyl-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

The reaction was run according to the procedure of Example 86.

25 MS (APCI), m/z ([M+H]⁺) 400.4.

EXAMPLE 96

6-(2-Benzenesulfonyl-ethyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

The reaction was run according to the procedure of Example 86.

5 MS (APCI), m/z ([M+H]⁺) 502.5.

EXAMPLE 97

8-Methyl-6-(3-methyl-but-2-enyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

The reaction was run according to the procedure of Example 86.

10 MS (APCI), m/z ([M+H]⁺) 402.4.

EXAMPLE 98

6-[2-(4-Fluoro-benzenesulfonyl)-ethyl]-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

The reaction was run according to the procedure of Example 86.

15 MS (APCI), m/z ([M+H]⁺) 520.5.

EXAMPLE 99

6-[3-(4-Fluoro-phenyl)-3-oxo-propyl]-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

The reaction was run according to the procedure of Example 86.

20 MS (APCI), m/z ([M+H]⁺) 484.4.

EXAMPLE 100

6-(2-Benzoylamino-ethyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

The reaction was run according to the procedure of Example 86.

25 MS (APCI), m/z ([M+H]⁺) 481.5.

EXAMPLE 101

8-Methyl-5,7-dioxo-6-(2-phenoxy-ethyl)-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

The reaction was run according to the procedure of Example 86.

5 MS (APCI), m/z ([M+H]⁺) 454.4.

EXAMPLE 102

6-(3,4-Dichloro-benzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide

Lithium hexamethyldisilazane (0.9 mL, 1 M in THF, 0.9 mmol) was added
10 to a solution of 6-(3,4-dichlorobenzyl)-thiazolo[3,2-c]pyrimidine-5,7-dione
(Example 12, Step A, 0.200 g, 0.61 mmol) in tetrahydrofuran (10 mL), under
nitrogen at -72°C. After 3 minutes, 1-isocyanatomethyl-4-methoxy-benzene
(0.22 mL, 1.5 mmol) was added. The reaction was stirred 15 minutes, then
aqueous ammonium chloride was added, and the reaction allowed to warm to
15 room temperature. EtOAc (50 mL) was added to the reaction, water layer was
removed, and the organic layer was, dried (Na_2SO_4) and evaporated. The residue
was chromatographed on silica gel eluting with CH_2Cl_2 : EtOAc, 9:1. The isolated
product was triturated with diethyl ether and dried in vacuum to give 45.2 mg
(15%) of 6-(3,4-dichlorobenzyl)-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-
c]pyrimidine-2-carboxylic acid 4-methoxy-benzylamide: mp 206-207° C;
20 MS (APCI+), m/z (%): 493(15), 492(80), 490(100), 329(40), 326(55), 263(30),
121(30).

EXAMPLE 103

4-[2-(4-Methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester

8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester

Step A: 8-Methyl-thiazolo[3,2-c]pyrimidine-5,7-dione (4.55 g, 25.0 mmol)
was suspended in dimethylformamide (100 mL) under a nitrogen atmosphere.
30 Cesium carbonate (8.96 g, 27.5 mmol) was added followed by 4-bromomethyl-

benzoic acid methyl ester (5.96 g, 26.0 mmol). The reaction was stirred at 50°C for 4 hours. The solvent was evaporated in vacuo. The resulting solid was triturated with diethyl ether to give 8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester (91%); MS (APCI+), m/z (%): 5 331(100), 661(15).

4-[2-(4-Methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester

Step B: The reaction was run as in Example 102 to give 4-[2-(4-methoxy-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-10 benzoic acid methyl ester (23%): mp 163-165° C. MS (APCI+), m/z (%): 494(100), 331(50), 121(40).

EXAMPLE 104

4-(8-Methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl)-benzoic acid tert-butyl ester

15 The reaction was run as in Example 103, Step A, using 4-bromomethyl-benzoic acid tert-butyl ester. 4-(8-Methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl)-benzoic acid tert-butyl ester was isolated (90%): mp 163-165° C. MS (APCI+), m/z (%): 373(90), 317(100).

EXAMPLE 105

20 **4-[2-(3-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester**

25 8-Methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester was treated as in Example 102 using 1-fluoro-3-isocyanatomethyl-benzene. The resulting solid was purified by flash chromatography on silica gel eluting with CH₂Cl₂:THF, 19:1 to give 4-[2-(3-fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester (36%): mp 209-211° C; MS (APCI+), m/z (%): 482(100), 331(75).

EXAMPLE 106

4-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester

8-Methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester was treated as in Example 102 using 1-fluoro-4-isocyanatomethyl-benzene. The resulting solid was purified by flash chromatography on silica gel eluting with CH₂Cl₂:tetrahydrofuran, 24:1 to give 4-[2-(4-fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidin-6-ylmethyl]-benzoic acid methyl ester (30%): mp >215°C; MS (APCI+), m/z (%): 482(100), 331(70).

EXAMPLE 107

6-(4-Cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

6-(4-Cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid

Step A: The product of Example 53, namely 8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione-2-carboxylic acid was reacted with 4-bromomethyl-benzonitrile according to the procedure of Example 103, Step A, to give 6-(4-cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (36%); MS (APCI+), m/z (%): 298(100).

6-(4-Cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

Step B: 6-(4-Cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid was treated as in Example 102 using 1-fluoro-4-isocyanatomethyl-benzene. The crude product was chromatographed on silica gel eluting with CH₂Cl₂:tetrahydrofuran, 19:1. The product was then triturated with diethyl ether and vacuum dried at room temperature to give 6-(4-cyano-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide (25%): mp >220°C; MS (APCI+), m/z (%): 449(100), 298(85).

EXAMPLE 108

8-Methyl-6-[4-(morpholine-4-sulfonyl)-benzyl]-thiazolo[3,2-c]pyrimidine-5,7-dione

The product from Example 53, namely 8-methyl-thiazolo[3,2-c]pyrimidine-5,7-dione (586 mg, 3.2 mmol),
5 4-morpholinosulfonylbenzyl bromide, (1.031 g, 3.2 mmol), cesium carbonate
(1.105 g, 3.4 mmol) and dimethylformamide (9 mL) were stirred at room
temperature overnight. The dimethylformamide was removed on the rotary
evaporator at 60°C. The residue was partitioned between ethyl acetate (200 mL)
10 and water (100 mL), the layers separated, the organic layer washed with brine
(50 mL) and dried over magnesium sulfate, filtered and concentrated to a tan
solid. Trituration with hexanes/ethyl acetate and filtration gave the product, 8-
methyl-6-[4-(morpholine-4-sulfonyl)-benzyl]-thiazolo[3,2-c]pyrimidine-5,7-
dione, as a tan solid, 1.195 g (88%). MS (APCI+), m/z (%): 422.1(100),
15 183.1 (25).

EXAMPLE 109

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-methoxy-benzylamide

The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-
20 6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (158 mg, 0.50 mmol)
was dissolved in dimethylformamide (4 mL). Added were 3-methoxybenzyl
amine (64 mg, 50 mmol), 1-hydroxybenzotriazole hydrate (68 mg, 0.50 mmol)
and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (100 mg,
0.52 mmol). The mixture was stirred overnight at room temperature. The reaction
25 mixture was concentrated on the rotary evaporator. The residue was partitioned
between ethyl acetate and water. The layers were separated, and the organic layer
was washed with water, saturated sodium bicarbonate solution, and brine. The
layers were separated, and the organic layer dried over magnesium sulfate,
filtered, and evaporated in vacuo. The residue was triturated with diethyl
ether/hexanes/ethyl acetate to give the product, 6-benzyl-8-methyl-5,7-dioxo-6,7-
30 dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 3-methoxy-benzylamide,
164 mg (75%). MS (APCI+), m/z (%): 436(100), 273(90).

EXAMPLE 110

6-Benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (tetrahydro-furan-2-ylmethyl)-amide

The product of Example 33, Step B, namely 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (158 mg, 0.50 mmol) was dissolved in dimethylformamide (4 mL). Added were tetrahydrofurfuryl amine (51 mg, 50 mmol), 1-hydroxybenzotriazole hydrate (68 mg, 0.50 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (100 mg, 0.52 mmol). The mixture was stirred 13 days at room temperature. The reaction mixture was concentrated on the rotary evaporator. The residue was partitioned between ethyl acetate and water. The layers were separated, and the organic layer was washed with water, saturated sodium bicarbonate solution, and brine. The layers were separated and the organic layer dried over magnesium sulfate, filtered, and evaporated in vacuo to give the product, 6-benzyl-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (tetrahydro-furan-2-ylmethyl)-amide, 147 mg (73%). MS (APCI+), m/z (%): 400(100), 273(50).

EXAMPLE 111

{5-[2-(4-Fluoro-benzylcarbamoyl)-8-methyl-5,7-dioxo-7H-thiazolo[3,2-c]pyrimidine-6-ylmethyl]-isoxazol-3-yl}-carbamic acid methyl ester

MS-APCI (M+1): 489.5

EXAMPLE 112

6-Benzyl-8-formyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

(1-Benzyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-ylsulfanyl)-acetic acid methyl ester

Step A: 3-Benzyl-6-chloro-1H-pyrimidine-2,4-dione (23.7 g, 100 mmol), methyl thioglycolate (11 mL, 123 mmol), and dimethylformamide (100 mL) were heated at 55°C for about one hour. Then triethylamine (15 mL, 108 mmol) was added, and the mixture heated at 70°C for 2 hours. The mixture was then stirred for 3 days at room temperature at which time more methyl thioglycolate (4.3 mL,

44.6 mmol) and triethylamine (94.5 mL, 30 mmol) were added, and the mixture was heated at 70°C for 1 hour. The volatiles were removed on a rotary evaporator (80°C), and the residue was partitioned between ethyl acetate (400 mL) and water (400 mL). The layers were separated, and the organic layer was washed with 10% aqueous citric acid solution (100 mL) and brine (100 mL), and dried over magnesium sulfate. The organic layer was filtered and concentrated. The aqueous washes were extracted again with ethyl acetate (400 mL) and the organic layer washed with brine (100 mL) and dried over magnesium sulfate, filtered and combined with the first ethyl acetate wash. The solution was concentrated to a yellow solid. The solid was triturated with ethyl acetate/hexanes (1:1), and the resulting solid collected by filtration; yield 18.6 g. MS (APCI+), m/z (%): 307.1(100), 275.0 (40).

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2,c]pyrimidine-2-carboxylic acid methyl ester

Step B: Neat dimethylformamide dimethylacetal (6 mL, 45 mmol) was added dropwise to a rapidly stirred solution of (1-benzyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-ylsulfanyl)-acetic acid methyl ester (6.12 g, 20 mmol) in tetrahydrofuran (250 mL) at 50°C. The solution was stirred at 50°C for 0.5 hour, and then was heated at 70°C on the rotary evaporator (no vacuum) until the solvent boiled off. More tetrahydrofuran (200 mL) was added, and the mixture was stirred overnight at room temperature. Dioxane (50 mL) was added, and the reaction mixture was concentrated to a brown oil. The oil was purified by filtration through silica gel (70-230 mesh) using ethyl acetate/hexanes (1:1) as eluant; yield 2.94 g (46%). MS (APCI+), m/z (%): 317.1(100), 259.0 (10).

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2,c]pyrimidine-2-carboxylic acid

Step C: 6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2,c]pyrimidine-2-carboxylic acid methyl ester (3.87 g, 12.2 mmol) was taken up in tetrahydrofuran (80 mL), and the solution was cooled to 0°C. A solution of lithium hydroxide hydrate (0.49 g, 11.9 mmol) in water (10 mL) was added dropwise over 3 minutes. The solution was stirred 12 minutes at 0°C, and was then poured into a separatory

funnel containing ethyl acetate (350 mL) and 10% citric acid solution (25 mL). The layers were separated, the organic layer washed with brine (50 mL), dried over magnesium sulfate, and filtered. The organic layer was concentrated on the rotary without heating. The residue was triturated with diethyl ether, and the solid 5 collected by filtration; yield 2.996 g (81%). MS (APCI+), m/z (%): 303.0 (20), 259.0 (100).

6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2,c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

Step D: 6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2,c]pyrimidine-2-carboxylic acid (2.25 g, 7.45 mmol) was mixed with 1-hydroxybenzotriazole (1.02 g, 7.55 mmol), 4-fluorobenzyl amine (0.95 g, 7.6 mmol), and dimethylformamide (12 mL), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.45 g, 7.6 mmol) was added. The mixture was stirred for 3 days at room temperature. The volatiles were removed on the rotary evaporator with a bath temperature at 65°C, and the resulting residue was partitioned between ethyl acetate (300 mL) and water. The organic layer was washed with water (100 mL), sodium bicarbonate solution (2 × 50 mL), and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to a solid, which was triturated with hexanes/diethyl ether. The 15 insoluble portion was collected by filtration, washed with diethyl ether, and dried; yield 2.599 g (85%). MS (APCI+), m/z (%): 410.0 (100), 259.0 (20).

6-Benzyl-8-formyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2,c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

Step E: 6-Benzyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2,c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide (2.09 g, 5.84 mmol) was taken up in dimethylformamide (7.5 mL), and phosphorus oxychloride (1.2 mL, 12.9 mmol) was added dropwise over 5 minutes. The reaction mixture was stirred for 0.5 hour at room temperature, and then for 1.5 hours at 75°C. No starting material remained by mass spectrum analysis. The reaction mixture was cooled to room 25 temperature, and was added dropwise to rapidly stirred water (150 mL). A yellow solid precipitated and was collected by filtration. The solid was taken up in ethyl 30

acetate/tetrahydrofuran, and the solution was dried over magnesium sulfate, filtered, and concentrated to a solid. The solid was triturated with hexanes/ethyl acetate and collected. The solid was slurried in ethyl acetate and collected; yield 0.665 g of 6-benzyl-8-formyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2,c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide. An additional 1.6 g of material was obtained in several portions by filtration through silica gel using dichloromethane/tetrahydrofuran, 95/5 as eluant. MS (APCI+), m/z (%): 438.0 (100), 287.0 (25).

10

EXAMPLE 113

6-Benzyl-8-hydroxymethyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2,c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide

A portion of the aldehyde prepared in Example 112, Step E, namely 6-benzyl-8-formyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2,c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide, (0.31 g, 0.71 mmol) was taken up in tetrahydrofuran (30 mL) and water (20 mL) containing sodium borohydride (0.21 g, 5.5 mmol), and the mixture was stirred at room temperature. After 0.5 hour, no starting material remained. The reaction was quenched by addition of 10% aqueous citric acid solution (5 mL). Brine (50 mL) was added, and the mixture was extracted with ethyl acetate (100 mL). The organic layer was washed with brine and dried over magnesium sulfate, filtered, and concentrated to a yellow oil. The oil was chromatographed on silica gel using ethyl acetate, then tetrahydrofuran as eluant; yield 0.024 g (6.5%) of 6-benzyl-8-hydroxymethyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2,c]pyrimidine-2-carboxylic acid 4-fluoro-benzylamide. MS (APCI-), m/z (%): 438.0 (50), 287.0 (100).

20

EXAMPLE 114

6-(3,4-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide hydrochloride

25

Step A: 8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide

8-Methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (3.61 g) was dissolved in DMF (20 mL). To the solution was added 1-hydroxybenzotriazole hydrate (2.15 g) and 2-methoxy-4-aminomethylpyridine, followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.05 g). The mixture was stirred at room temperature overnight. The DMF was removed in vacuum at 60° C. The residue was stirred in water, and the water was decanted. The residue was again stirred with water, and the resulting solid filtered. The solid was stirred with aqueous sodium bicarbonate, filtered, and air dried to give 8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide (59% yield); MS (APCI+), m/z (%): 347(20), 174(100), 135(20), 128(65).

15 **Step B: 6-(3,4-Fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide hydrochloride**

The product of Step (A), namely 8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide (200 mg, 0.58 mmol), was suspended in DMF (10 mL), and cesium carbonate (204 mg, 0.63 mmol) was added, followed by 3,4-difluorobenzyl bromide (0.08 mL, 0.63 mmol). After 17 hours, the DMF was removed in a vacuum at 70° C. The residue was mixed with THF and filtered through a pad of Celite over silica gel eluting with additional THF. The filtrate was evaporated in vacuo to an oil. The material was purified by chromatography on silica gel, eluting with CH₂Cl₂:THF (9:1) to give 6-(3,4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-methoxy-pyridin-4-ylmethyl)-amide (30% yield). The residue was dissolved in THF (2 mL) and treated with HCl/diethyl ether (1 M, 0.2 mL). The resulting solid was isolated by filtration and dried in a vacuum at 55°C to give 6-(3,4-fluoro-benzyl)-8-methyl-5,7-dioxo-6,7-dihydro-5H-thiazolo[3,2-c]pyrimidine-2-carboxylic acid (2-

methoxy-pyridin-4-ylmethyl)-amide hydrochloride; MS (APCI+), m/z (%): 473(100), 309(30).

The invention compounds of Formula I have been evaluated in standard assays for their ability to inhibit the catalytic activity of various MMP enzymes. 5 The assays used to evaluate the biological activity of the invention compounds are well-known and routinely used by those skilled in the study of MMP inhibitors and their use to treat clinical conditions.

The assays measure the amount by which a test compound reduces the hydrolysis of a thiopeptolide substrate catalyzed by a matrix metalloproteinase 10 enzyme. Such assays are described in detail by Ye et al., in *Biochemistry*, 1992;31(45):11231-11235, which is incorporated herein by reference.

Thiopeptolide substrates show virtually no decomposition or hydrolysis at or below neutral pH in the absence of a matrix metalloproteinase enzyme. A typical thiopeptolide substrate commonly utilized for assays is Ac-Pro-Leu-Gly-thioester-Leu-Leu-Gly-OEt. A 100 μ L assay mixture will contain 50 mM of N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid buffer ("HEPES," pH 7.0), 15 10 mM CaCl₂, 100 μ M thiopeptolide substrate, and 1 mM 5,5'-dithio-bis-(2-nitrobenzoic acid) (DTNB). The thiopeptolide substrate concentration may be varied, for example from 10 to 800 μ M to obtain K_m and K_{cat} values. The change in 20 absorbance at 405 nm is monitored on a Thermo Max microplate reader (molecular Devices, Menlo Park, CA) at room temperature (22°C). The calculation of the amount of hydrolysis of the thiopeptolide substrate is based on E₄₁₂ = 13600 M⁻¹ cm⁻¹ for the DTNB-derived product 3-carboxy-4-nitrothiophenoxide. Assays are carried out with and without matrix 25 metalloproteinase inhibitor compounds, and the amount of hydrolysis is compared for a determination of inhibitory activity of the test compounds.

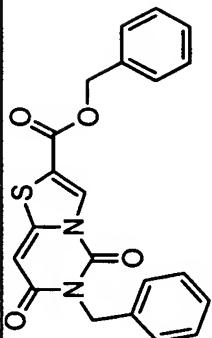
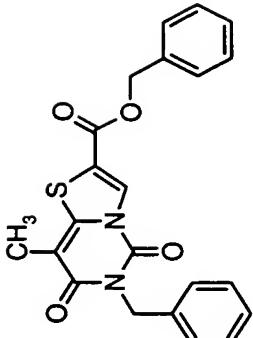
Several representative compounds have been evaluated for their ability to inhibit various matrix metalloproteinase enzymes. Table 1 below presents inhibitory activity for compounds from various classes. In Table 1, MMP-1FL refers to full length interstitial collagenase; MMP-2FL refers to full length Gelatinase A; MMP-3CD refers to the catalytic domain of stromelysin-1; 30 MMP-7FL refers to full length matrilysin; MMP-9FL refers to full length

Gelatinase B; MMP-13CD refers to the catalytic domain of collagenase 3; and MMP-14CD refers to the catalytic domain of MMP-14. Test compounds were evaluated at various concentrations in order to determine their respective IC₅₀ values, the micromolar concentration of compound required to cause a 50% inhibition of catalytic activity of the respective enzyme.

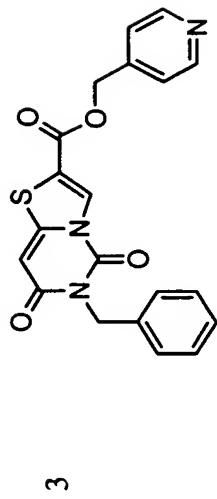
5

It should be appreciated that the assay buffer used with MMP-3CD was 50 mM N-morpholinoethane sulfonate ("MES") at pH 6.0 rather than the HEPES buffer at pH 7.0 described above.

Table 1. IC₅₀ (μM) Versus Certain MMPs

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
1		0.0285	>100	>100	23	96	>100	>30
2		0.0056	>100	>100	>30	>100	>100	>100

ClH.



0.0054 >100 11 >100 >100 >100

Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	CD	FL	FL	FL	CD
4		0.5725	81	>100	27	65	83.5	47.5
5		14.3333	>100	>100	>100	>100	>100	>100

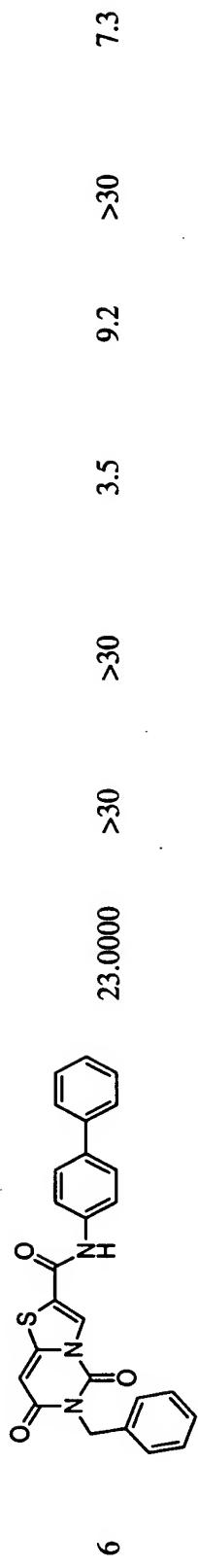
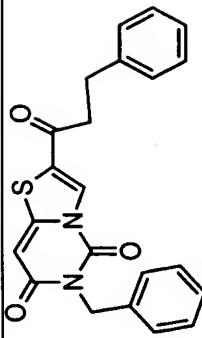


Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
8		6.6	>100	>100	3.2	>30	>100	8.8

Example No.	Structure	MMP-13 CD	MMP-01 FL	MMP-02 FL	MMP-03 CD	MMP-07 FL	MMP-09 FL	MMP-14 CD
9		0.4900 >100	>100 68	>100 >100	>100 >100	>100 21	>30 21	>30 >30
10		0.1200 >30	>100 >30	>100 >30	>30 21	>30 21	>30 21	>30 >30

Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

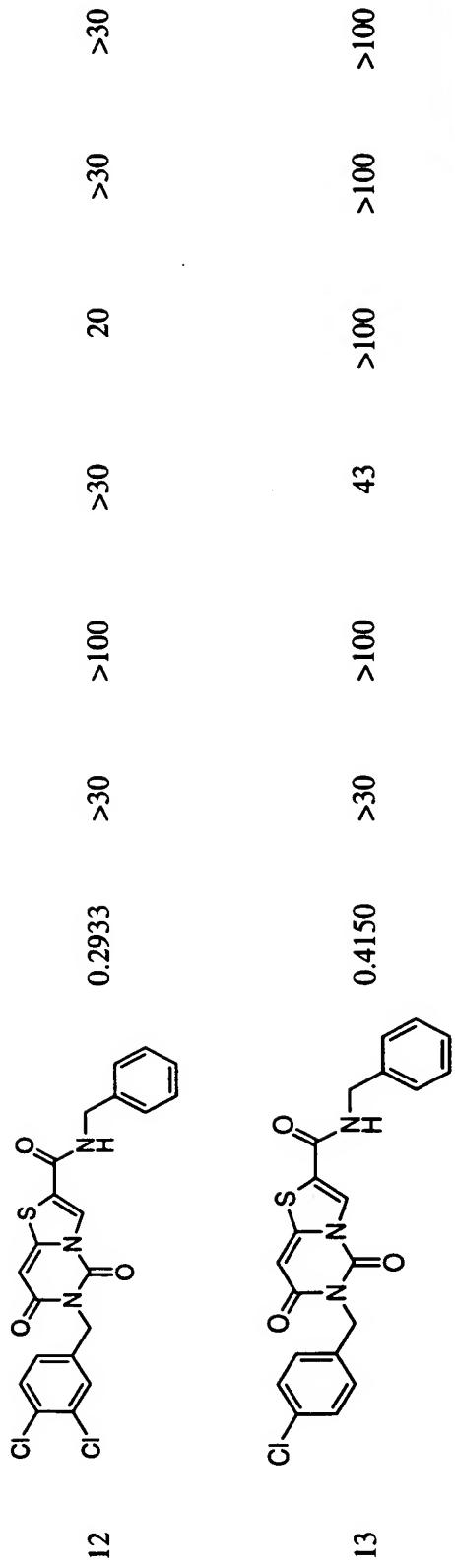
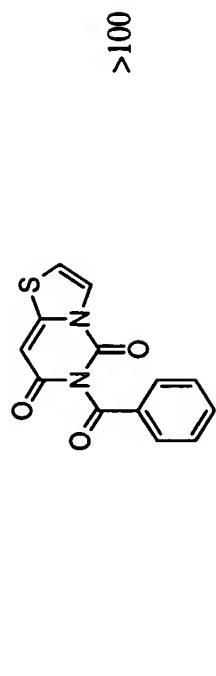
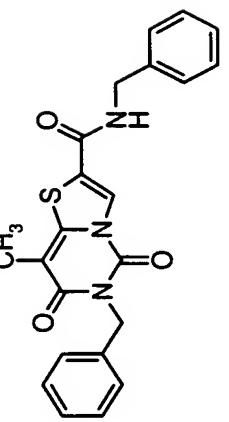
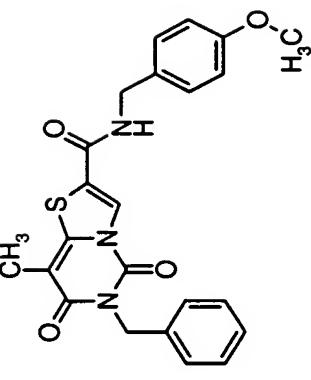
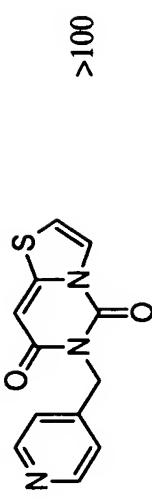


Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
16		0.0940	>100	>100	51	>30	>100	>30
17		0.0217	>30	>30	16	>30	>30	>30



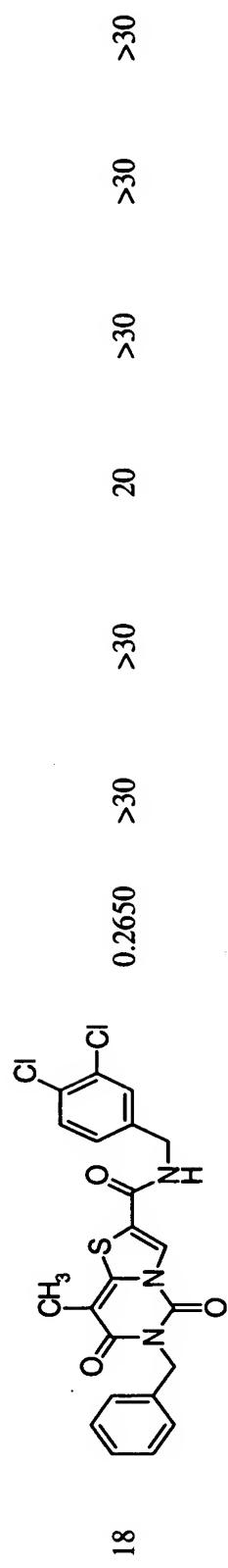
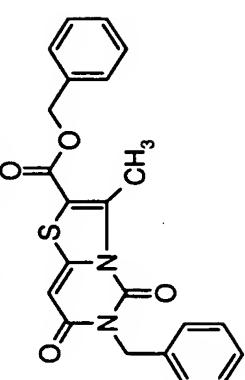
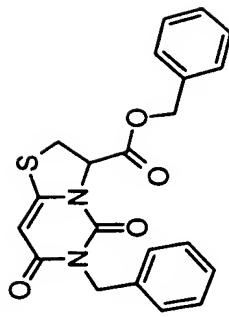
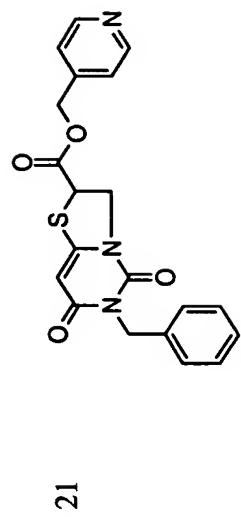


Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
19		21.0000	>100	>100	>100	8.8	>30	>30
20					none			

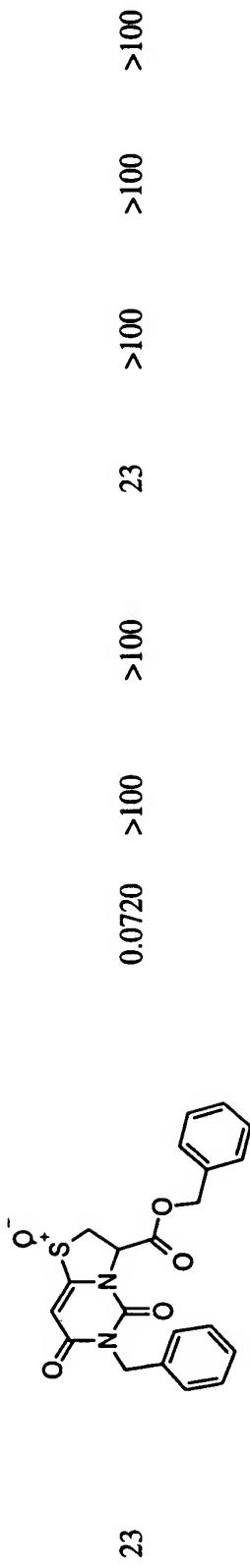
CIH



6.5000 >100 >100 >100 >100 >100 >100

Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
21		0.5900	>100	>100	>100	>100	>100	>100
22								



35^a >100

Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13 CD	MMP-01 FL	MMP-02 FL	MMP-03 CD	MMP-07 FL	MMP-09 FL	MMP-14 CD
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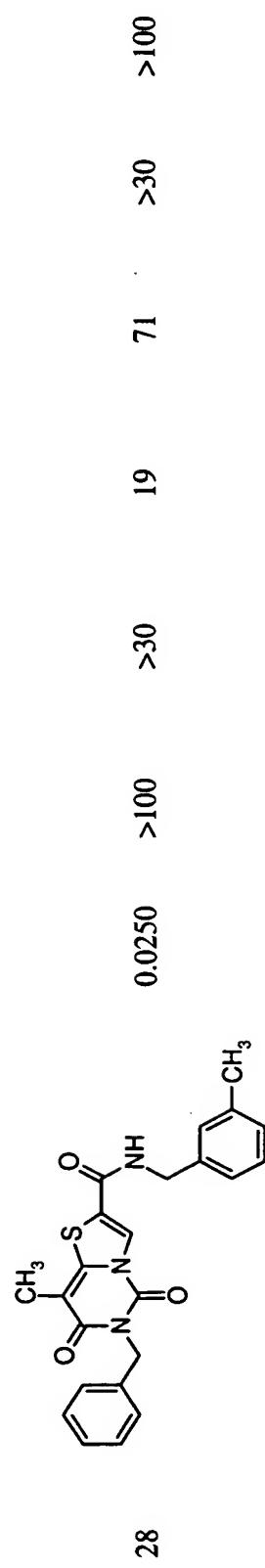
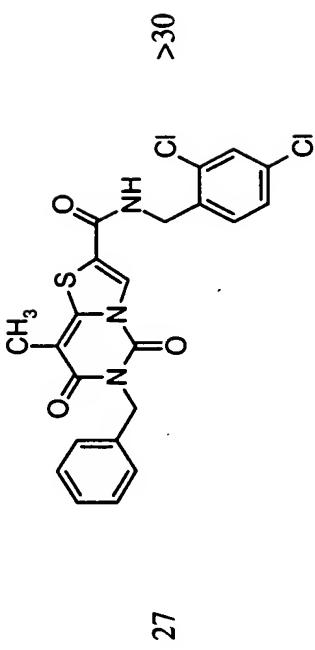
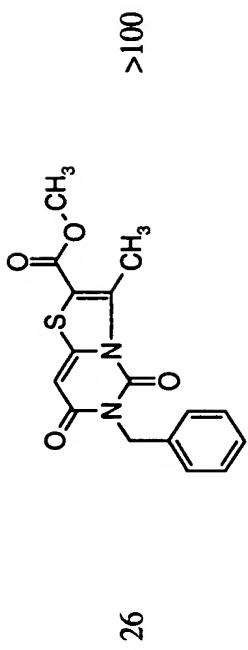
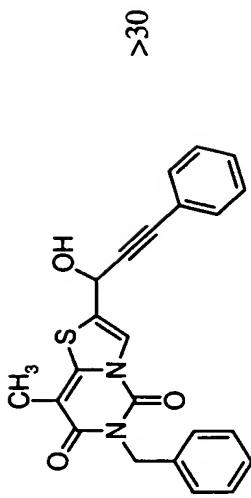


Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
29		25						
30					0.0245	>30	>100	>30

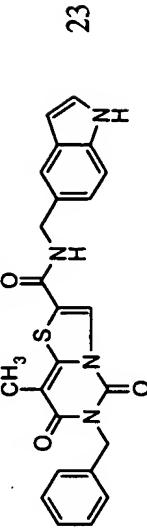
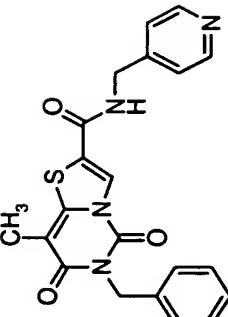


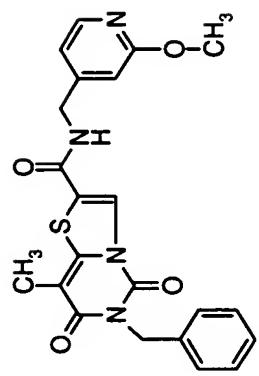
31

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
32		0.0224	>100	>100	11	>30	>100	>30
33		>100						
33a						none		

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
34								
36		0.0487	>30	>100	>30	>100	>30	>100



0.0175 >30 10 >30 >30 >30

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
37a		0.0208	>30	>30	20.5	26	>30	>30
38					25			

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
39					2.2999			
40						>100		

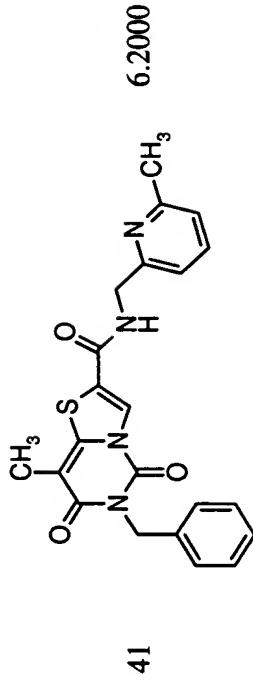
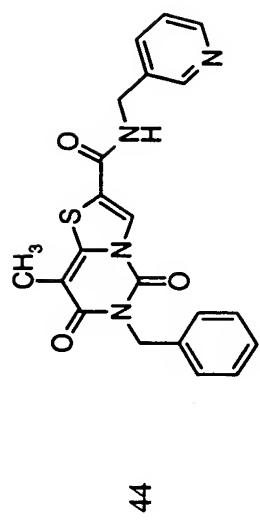


Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

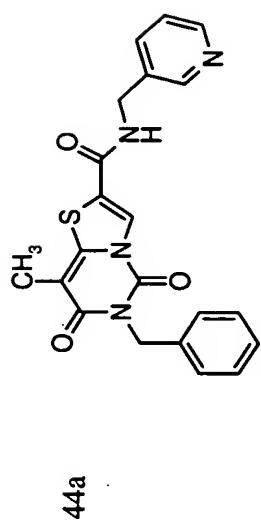
Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	CD	FL	FL	FL	CD
42		0.0046	>30	>30	10	>30	>30	>100
43		0.0290	>100	>30	>30	>30	>30	>100



0.2250 >100 >100 >30 >100 >30 >100

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13 CD	MMP-01 FL	MMP-02 FL	MMP-03 CD	MMP-07 FL	MMP-09 FL	MMP-14 CD
44	C <small>H</small>							



0.2600 >30 >100 >30 >100 >30 >100

氯化物
溴化物
碘化物
氟化物
硝酸盐
硫酸盐
碳酸盐
磷酸盐
乙酸盐
氯化物
溴化物
碘化物
氟化物
硝酸盐
硫酸盐
碳酸盐
磷酸盐
乙酸盐

ClH

45

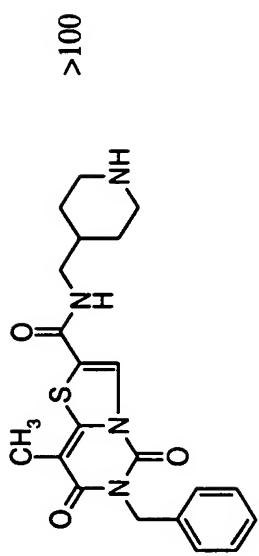


Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

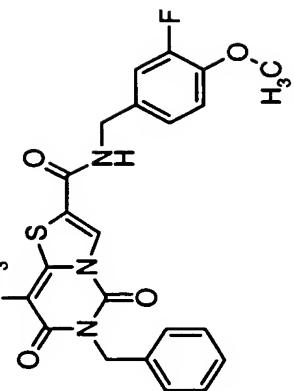
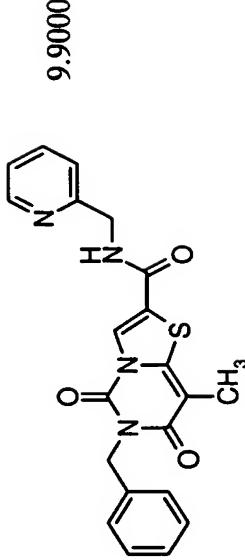
Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
46		0.0250	>100	>100	12	>30	>100	>100
47		C1H				9.9000		

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

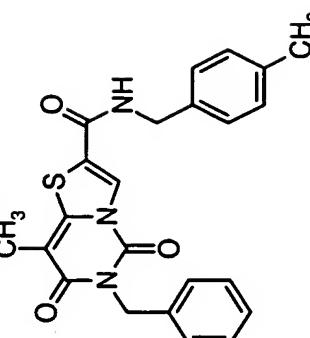
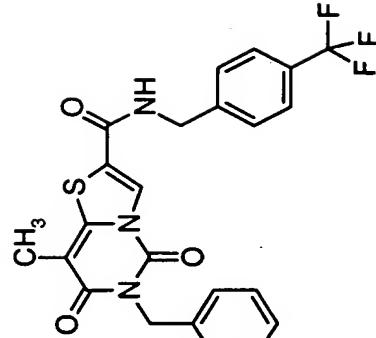
Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
48		0.2250	>30	>30	19	28	>100	>100
49		2.21	>30	>30	>100	>100	>100	>100

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	CD	CD	FL	FL	CD
50		0.0869	>30	23	31	>100	>100	>100
51		0.8150	>30	>30	>100	>30	>100	>100

Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13 CD	MMP-01 FL	MMP-02 FL	MMP-03 CD	MMP-07 FL	MMP-09 FL	MMP-14 CD
52						>100		
53						>100		

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
55		0.0015	>100	>100	29	>100	>100	>100
56		0.00175	>100	>100	36	>100	>100	>100

Table 1. IC₅₀ (μ M) Versus Certain MAMPs (Cont'd)

Example No.	Structure	MMP-13 CD	MMP-01 FL	MMP-02 CD	MMP-03 FL	MMP-07 FL	MMP-09 FL	MMP-14 CD
57		0.0455	>30	>30	>100	>30	>30	>30
58		0.002225	>100	>100	68	>100	>100	>100

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

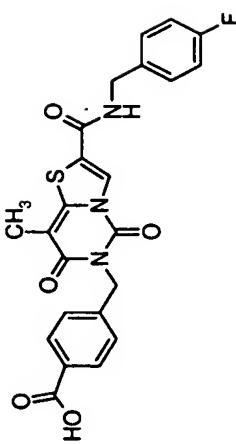
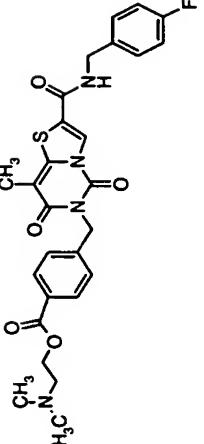
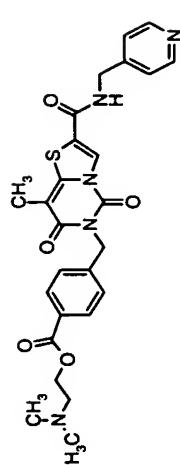
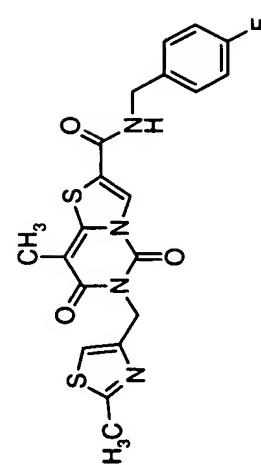
Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
59		0.0020	>100	>100	55.5	>100	>100	>100
60		0.094	>100	>100	>30	>100	>100	>100

Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
63		0.2350	>100	>100	>100	>100	>100	>100
64		0.7700	>100	>100	>30	>100	>30	>100

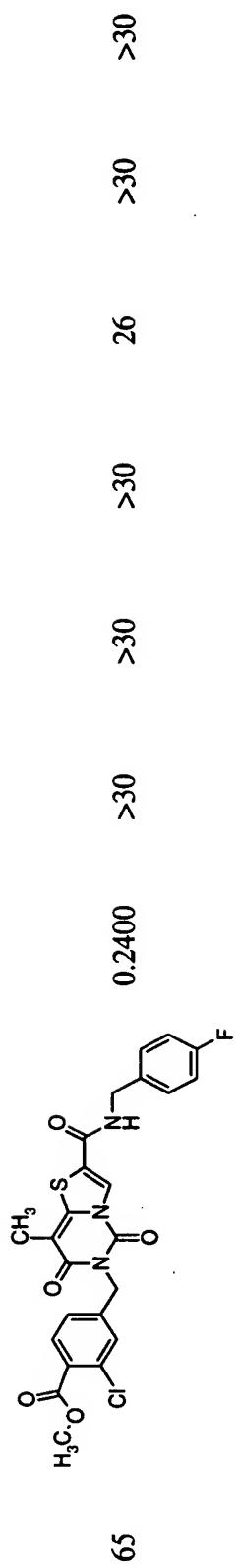


Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
66								
67		0.5300	>100	>100	>30	>100	>100	>100
68		0.0180	>100	>100	18	>100	>100	>100

Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	CD	FL	FL	FL	CD
73		0.0370	>100	>100	>100	>100	>100	>30
74		0.2050	>30	>30	>30	87	>30	>30

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

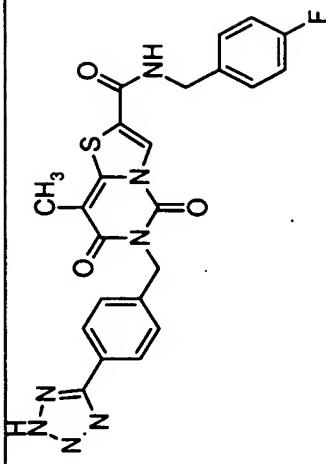
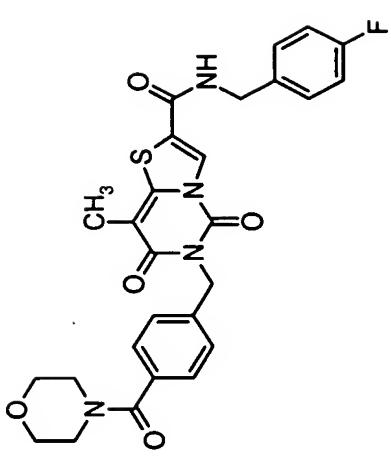
Example No.	Structure	MMP-13 CD	MMP-01 FL	MMP-02 FL	MMP-03 CD	MMP-07 FL	MMP-09 FL	MMP-14 CD
75		0.0009	>100	>100	16	>100	>100	>100
76		0.0110	>30	>30	>30	>30	>30	>30

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

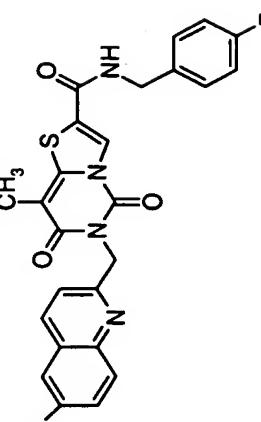
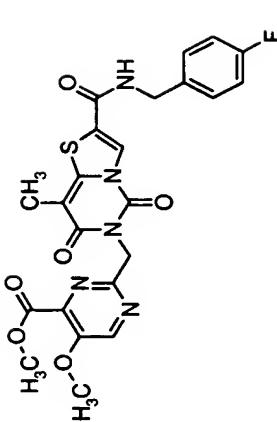
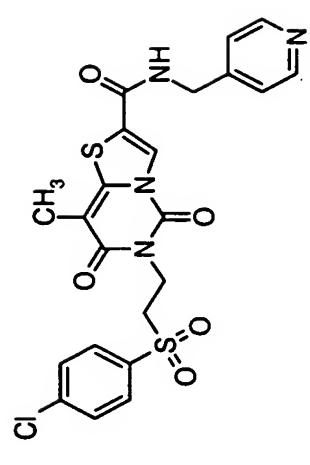
Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	CD	FL	FL	FL	CD
77		0.0860	>30	>30	18	>30	>30	>30
78		1.8500	>30	>30	>30	>30	>30	>30

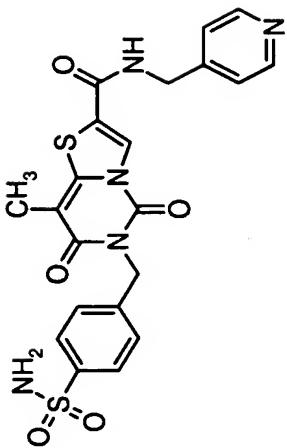
Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure CIH	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
83					2.6000			

CIH



84

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Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
	CD	FL	FL	CD	FL	FL	FL	CD
85		0.054667	>30	>30	>30	>30	>30	>30
86		0.3500						

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

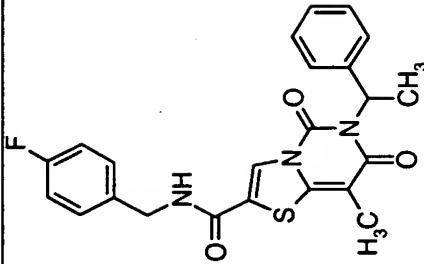
Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
87				2.1000				

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

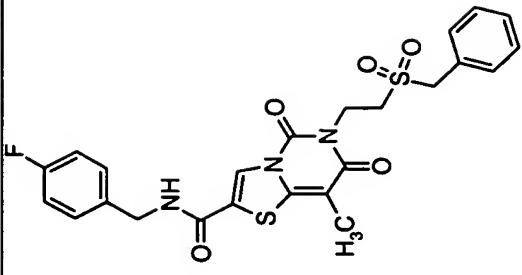
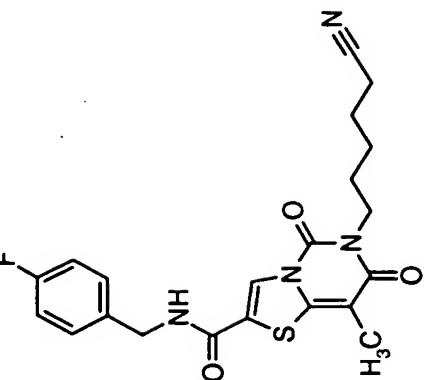
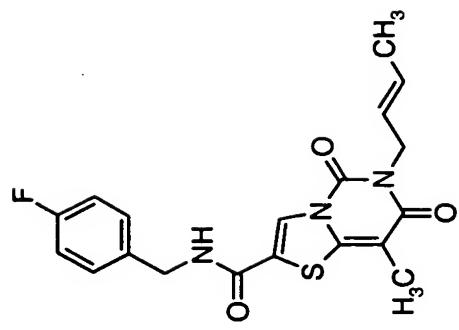
Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
88					0.5600			

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13 CD	MMP-01 FL	MMP-02 FL	MMP-03 CD	MMP-07 FL	MMP-09 FL	MMP-14 CD
89					1.0850			

0.5300



90

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

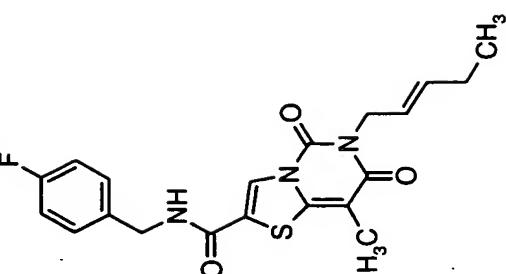
Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
91					0.1600			

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

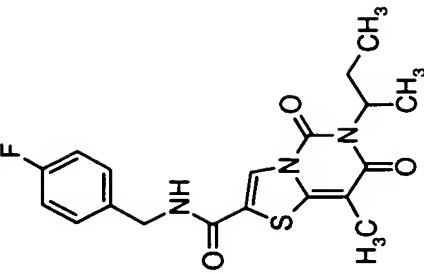
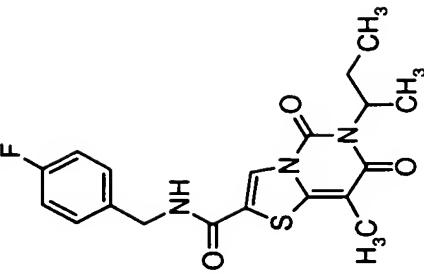
Example No.	Structure	MMP-13 CD	MMP-01 FL	MMP-02 FL	MMP-03 CD	MMP-07 FL	MMP-09 FL	MMP-14 CD
92			0.4000					

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

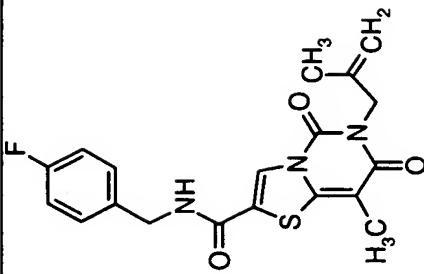
Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
93					1.5500			

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

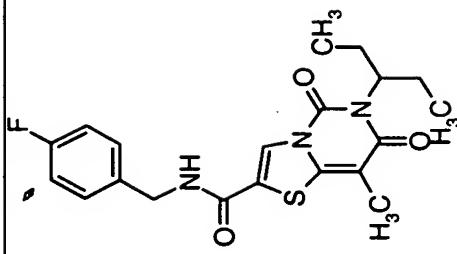
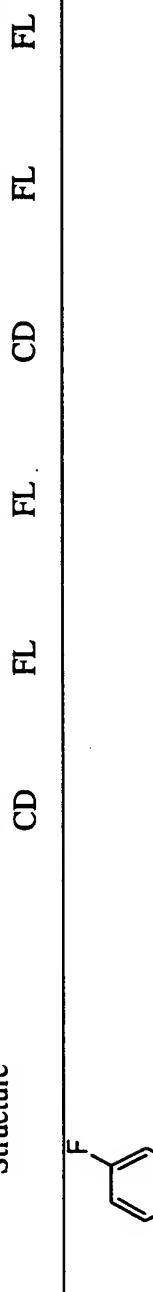
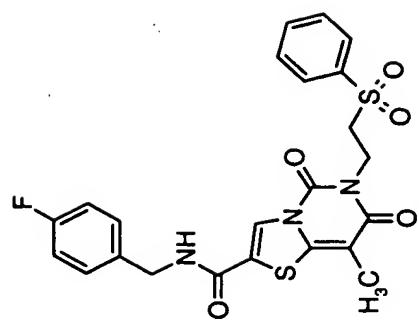
Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
94				>30				

Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

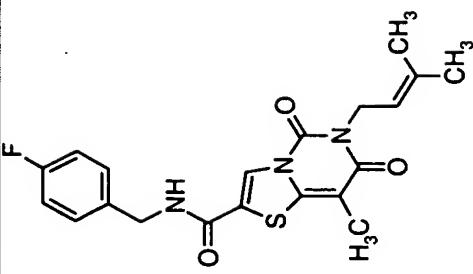
Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
95	 <chem>CC#C[C@H]1C(=O)N(C)C(=O)N2=C(C=C(C=C2S=C(NC)Cc3ccccc3F)C(=O)C)C1</chem>						0.0920	

1.2000



96

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13 CD	MMP-01 FL	MMP-02 CD	MMP-03 FL	MMP-07 FL	MMP-09 FL	MMP-14 CD
97					0.8200			

0.6450

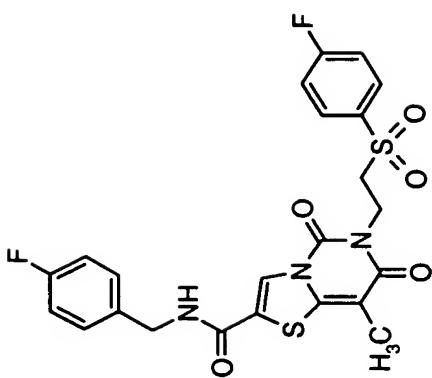


Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	CD	FL	FL	FL	CD
99			0.5100					

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

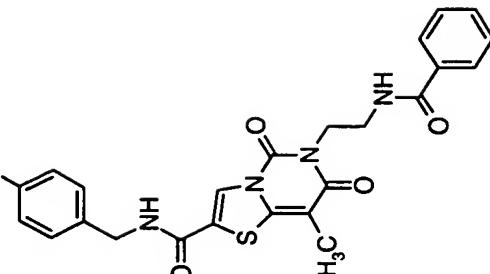
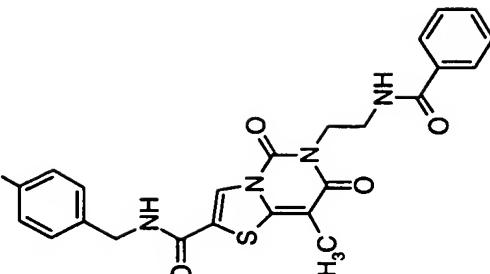
Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
100						10.0		

Table 1. IC₅₀ (μ M) Versus Certain MAMPs (Cont'd)

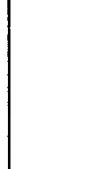
Example No.	Structure	MMP-13 CD	MMP-01 FL	MMP-02 FL	MMP-03 CD	MMP-07 FL	MMP-09 FL	MMP-14 CD
101		0.0580						
102						0.0840	>100	>100

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
103		0.01065	>100	65	65	>100	>100	>100
104					>30			
105		0.0715	>30	>30	19	27	>30	>30

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

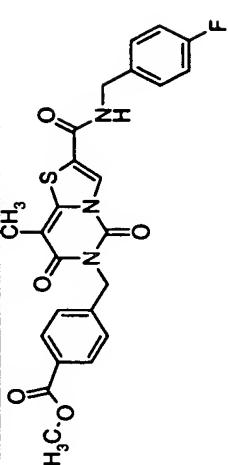
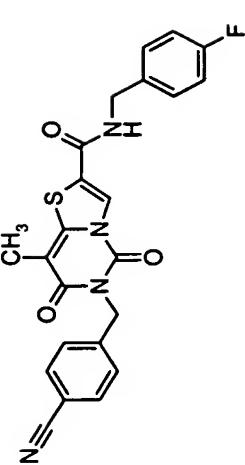
Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	CD	FL	FL	FL	CD
106		0.0180	>100	>30	17	>30	>100	>100
107		0.023	>100	>30	25	>30	>30	>30

Table 1. IC₅₀ (μM) Versus Certain MMPs (Cont'd)

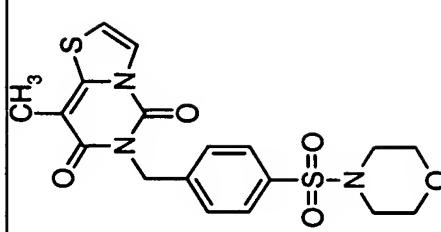
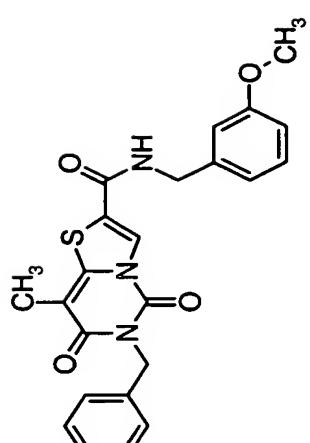
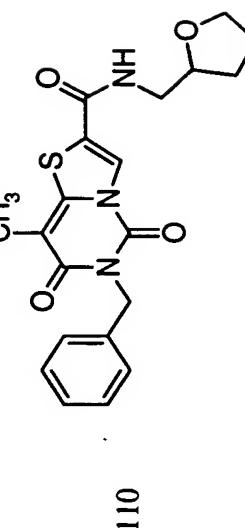
Example No.	Structure	MMP-13	MMP-01	MMP-02	MMP-03	MMP-07	MMP-09	MMP-14
		CD	FL	FL	CD	FL	FL	CD
108				>100				
109					0.0060	>30	>30	>30

Table 1. IC₅₀ (μ M) Versus Certain MMPs (Cont'd)

Example No.	Structure	MMP-13 CD	MMP-01 FL	MMP-02 FL	MMP-03 CD	MMP-07 FL	MMP-09 FL	MMP-14 CD
110								

(a) This entry is for Example 35, not Example 25.

Further, IC₅₀ inhibition of MMP-13CD by the compounds of Examples 111 and 114 is 0.17 micromolar and 0.0155 micromolar, respectively.

The foregoing data establish that the invention compounds of Formula I are potent inhibitors of MMP enzymes, and are especially useful due to their 5 selective inhibition of MMP-13. Because of this potent and selective inhibitory activity, the invention compounds are especially useful to treat diseases mediated by the MMP enzymes, and particularly those mediated by MMP-13.

Administration of a compound of Formula I, or a pharmaceutically acceptable salt thereof, to a mammal to treat the diseases mediated by MMP 10 enzymes is preferably, although not necessarily, accomplished by administering the compound, or the salt thereof, in a pharmaceutical dosage form.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, 15 intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise 20 as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I. The active compound generally is present in a concentration of about 5% to about 95% by weight of the formulation.

For preparing pharmaceutical compositions from the compounds of the 25 present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, 30 or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from 5% or 10% to about 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors,

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stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 1 to 1000 mg, preferably 10 to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as agents to inhibit a matrix metalloproteinase enzyme for the treatment of atherosclerotic plaque rupture, aortic aneurism, heart failure, restenosis, periodontal disease, corneal ulceration, cancer metastasis, tumor angiogenesis, arthritis, or other autoimmune or inflammatory disorders dependent upon breakdown of connective tissue, the compounds utilized in the pharmaceutical method of this invention are administered at a dose that is effective to inhibit the hydrolytic activity of one or more matrix metalloproteinase enzymes. The initial dosage of about 1 mg/kg to about 100 mg/kg daily will be effective. A daily dose range of about 25 mg/kg to about 75 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired. Typical dosages will be from about 0.1 mg/kg to about 500 mg/kg, and ideally about 25 mg/kg to about 250 mg/kg, such that it will be an amount which is effective to treat the particular disease being prevented or controlled.

The following examples illustrate typical formulations provided by the invention.

FORMULATION EXAMPLE 1

Tablet Formulation

Ingredient	Amount (mg)
Bicyclic pyrimidine of Example 3	25
Lactose	50
Corn starch (for mix)	10
Corn starch (paste)	10
Magnesium stearate (1%)	5
Total	100

5 The bicyclic pyrimidine of Example 3, lactose, and corn starch (for mix) are blended to uniformity. The corn starch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate
10 and pressed into a tablet. Such tablets can be administered to a human from one to four times a day for treatment of atherosclerosis and arthritis.

FORMULATION EXAMPLE 2

Preparation for Oral Solution

Ingredient	Amount
Bicyclic pyrimidine of Example 4	400 mg
Sorbitol solution (70% N.F.)	40 mL
Sodium benzoate	20 mg
Saccharin	5 mg
Red dye	10 mg
Cherry flavor	20 mg
Distilled water q.s.	100 mL

The sorbitol solution is added to 40 mL of distilled water, and the bicyclic pyrimidine of Example 4 is dissolved therein. The saccharin, sodium benzoate, flavor, and dye are added and dissolved. The volume is adjusted to 100 mL with distilled water. Each milliliter of syrup contains 4 mg of invention compound.

5

FORMULATION EXAMPLE 3

Parenteral Solution

In a solution of 700 mL of propylene glycol and 200 mL of water for injection is suspended 20 g of the compound of Example 17. After suspension is complete, the pH is adjusted to 6.5 with 1N sodium hydroxide, and the volume is made up to 1000 mL with water for injection. The formulation is sterilized, filled into 5.0-mL ampoules each containing 2.0 mL, and sealed under nitrogen.

As matrix metalloproteinase inhibitors, the compounds of Formula I are useful as agents for the treatment of multiple sclerosis. They are also useful as agents for the treatment of atherosclerotic plaque rupture, restenosis, periodontal disease, corneal ulceration, treatment of burns, decubital ulcers, wound repair, heart failure, cancer metastasis, tumor angiogenesis, arthritis, and other inflammatory disorders dependent upon tissue invasion by leukocytes.

It should be appreciated that in all invention embodiments described above or in the claims below, whenever an R group such as, for example, R¹, R², R³, R⁴, R⁵, or R⁶, is used more than once to define an invention compound, each use of the R group is independent of any other use of that same R group or, for that matter, any other R group, unless otherwise specified.

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